Kuwait Pharmacy Bulletin
DRUG INFORMATION FOR THE HEALTH PROFESSIONAL
Vol 18. No 4 Winter 2014 ISSN 1028-0480

Phosphodiesterase inhibitors and chronic obstructive pulmonary disease

Cyclic nucleotide phosphodiesterases (PDE) are enzymes that play a critical role in intracellular signaling by regulating cellular levels of adenosine and/or guanosine 3', 5' cyclic monophosphate (cAMP & cGMP) by selective hydrolysis of the 3' cyclic phosphate bonds to yield inactive 5'-AMP and 5'-GMP (Fig.1). cAMP and cGMP play a critical role in immune and inflammatory responses, smooth muscle relaxation, heart rate and contractility, visual phototransduction, cognition and memory function, and oocyte maturation[1]. They regulate protein kinase A (PKA), protein kinase G (PKG), cAMP activated exchange proteins, and cyclic nucleotide-gated channels (CNG) that work as photoreceptors after activation by cAMP and cGMP [2].

Phosphodiesterase enzyme family

There are 11 PDE families classified on the basis of their structure, substrate affinity, inhibitor selectivity, and their regulation by specific activators. Different mammalian PDEs share common structural determinants, catalytic core and regulatory regions. The catalytic domain in the C-terminal half comprises a region of ~ 270 amino acids with sequence identity common to all PDE families. It also includes two Zn^{2+} and Mg^{2+} binding sites for metal ion phosphohydrolases[2].

The protein domains, located between the N- terminal and the catalytic core, are called the regulatory region; this contains calmodulin binding sites unique for PDE1, PAS (per–arnt–sim) domain for PDE8, and upstream conserved regions in PDE4 (UCRs). GAF (allosteric cGMP binding site domains) are located in the regulatory region of PDE2, PDE5, PDE6, PDE10, and PDE11. This region contains phosphorylation sites for PDE1, PDE3, PDE4, PDE5 and PDE10, and phosphatidic binding site for PDE4[3].

PDE1

PDE1 is the unique PDE family that is activated via calmodulin in a calcium-dependent manner after complexation with four Ca^{2+} molecules. It is encoded by three genes: PDE1A, PDE1B, and PDE1C. PDE1A and PDE1B show high affinity for cGMP, whereas PDE1C shows high affinity for both cAMP and cGMP. PDE1 is mainly expressed in brain, heart and smooth muscles[4].

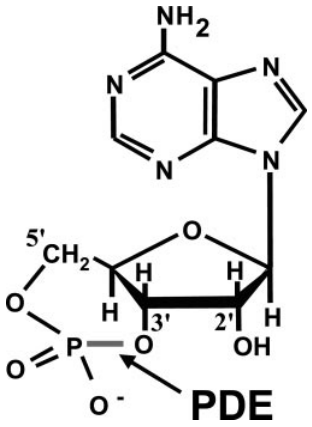


Fig 1. Phosphodiesterases hydrolyse the 3'-5' cyclic phosphate bond[1]

PDE2

PDE2 is encoded by three variant genes: PDE2A1, PDE2A2, and PDE2A3. It hydrolyzes both cGMP and cAMP. There are two cGMP -binding domains in its N-terminal domain, named GAF-A and GAF-B. PDE2 is allosterically and positively stimulated in response to elevated cGMP[2]. PDE2 is found in adrenal medulla, heart, brown adipose tissue, liver and brain[2].

PDE3

PDE3 is encoded by two genes: PDE3A and PDE3B. It has the capacity to hydrolyze both cAMP and cGMP with a higher affinity to cAMP, while cGMP behaves

In this issue

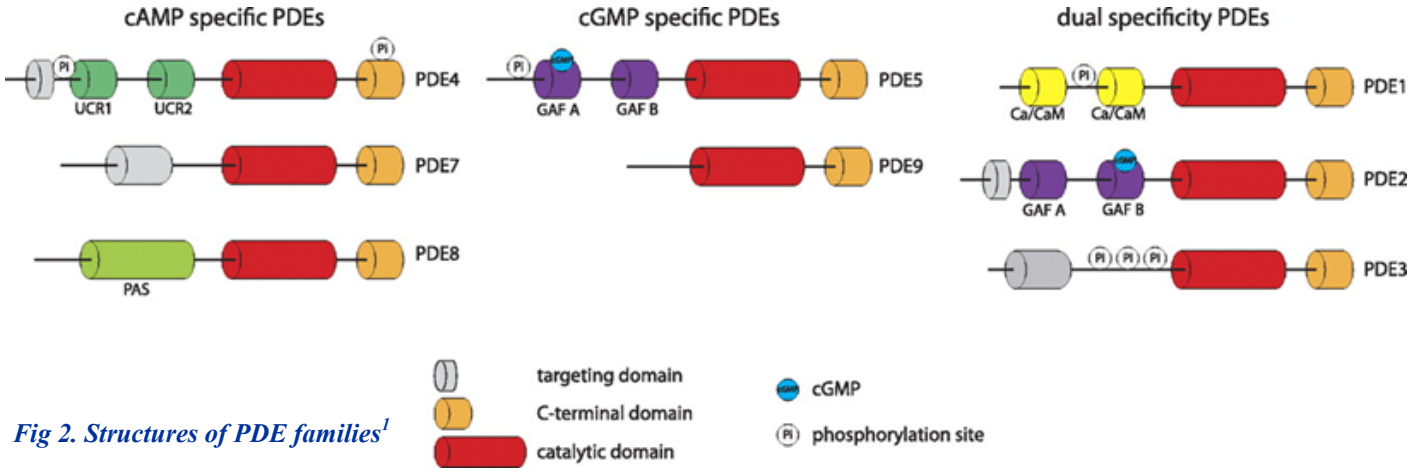


Fig 2. Structures of PDE families[1]

as a competitive inhibitor. PDE3A is mainly present in the heart, platelets, vascular smooth muscle and oocytes, while PDE3B is in adipocytes, hepatocytes and spermatocytes[2].

PDE4

PDE4 is encoded by four genes PDE4A, PDE4B, PDE4C and PDE4D. PDE4 is mainly expressed in the brain, inflammatory cells, heart and smooth muscles. This family appears to be an important target for anti-inflammatory drugs in asthma, COPD and rhinitis. PDE4A, PDE4B and PDE4D, are expressed in T cells, B cells, eosinophils, neutrophils, monocytes and macrophages, while PDE4C is minimally expressed. The four subfamily isozymes contain unique amino acid upstream conserved regions 1 and 2 (UCR1 & UCR2). These are classified into three sub-groups[4]. The long forms contain both UCR1 and UCR2; the short forms lack UCR1 and the super-short forms contain only the C-terminal portion of UCR2. (Fig. 3).

UCR2 has an auto-inhibitory nature and its removal has been shown to cause an increase in the catalytic activity of the enzyme, while UCR1 contains protein kinase A (PKA), a phosphorylation site, which activates PDE4 in response to the direct binding of cAMP and PDE4 serine residue phosphorylation[5].

PDE5

PDE5 has one encoded gene, PDE5A, with three variants (PDE5A1, PDE5A2, and PDE5A3) that are cGMP specific. PDE5 is mainly expressed in lungs, smooth muscles, corpus cavernosum, and involved in NO-cGMP signaling in platelets, to control aggregation. cGMP leads to smooth muscle relaxation in blood vessels supplying the corpus cavernosum, resulting in increased blood flow and penile erection. Therefore, PDE5 inhibitors such as Sildenafil and Tadalafil treat erectile dysfunction through increasing cGMP levels[2].

PDE6

PDE6, cGMP specific, is a key component in the visual transduction process. PDE6 is highly expressed in mammalian retina, in which a photon is absorbed by the photo pigments activating transducin (G-protein) via GDP-GTP exchange. The light-activated transducin stimulates PDE6 activity and induces the closure of cyclic nucleotide-gated channels (CNGC), thereby converting a light signal into an electrical signal. No specific PDE6 inhibitors have been identified until now; however, some PDE5 inhibitors can induce visual disturbances through PDE6 inhibition[4].

PDE7

PDE7 family specifically hydrolyses cAMP, has 2 genes encoding PDE7A and PDE7B with different variants. It does not contain GAF or regulatory domains; however, there are PKA phosphorylation sites in the N-terminal region. PDE7A1 expression has been detected in T-cell lines, peripheral blood T -lymphocytes, epithelial cell lines, airway and vascular smooth muscle cells, lung fibroblasts and eosinophils but not neutrophils, whereas, PDE7A2 is present in skeletal and cardiac muscles[2,4]. PDE7B1 mRNA is expressed in the heart, brain, lung, kidney, liver and muscle while PDE7B2 mRNA is restricted to testis, and PDE7B3 mRNA is observed in the heart[1].

PDE8

PDE8 family is cAMP-specific and encoded by PDE8A and PDE8B genes. PDE8A mRNA is highly expressed in the testis, the eye, liver, skeletal muscle, heart, kidney, ovary and brain. PDE8A1

protein has been detected in primary T lymphocytes and T cell lines and is found to be up-regulated after CD3/CD28 T lymphocyte stimulation. PDE8B1 expression is much higher in the thyroid gland than the brain, while PDE8B3 is mainly expressed in the brain[2,4].

PDE9

PDE9 specifically hydrolyzes cGMP, and is encoded by one gene, PDE9A expressed in kidney, brain, spleen, GI and prostate[1].

PDE10

PDE10 family is encoded by PDE10A gene and hydrolyses both cGMP and cAMP. PDE10A includes two GAF domains in the N-terminal region (GAF-A & GAF-B); in contrast to other PDEs, the GAF-A domain highly favours cAMP binding, which inhibits cGMP hydrolysis. PDE10A is expressed mainly in brain and testis[2,4].

PDE11

PDE11 is recently identified. PDE11A is the only identified gene with four different variants; PDE11A1 to PDE11A4. PDE11A contains 2 GAF domains and hydrolyzes both cAMP and cGMP [2,3]. PDE11A1 is expressed in skeletal muscle, while PDE11A3 in testis, and PDE11A4 in prostate gland. Tadalafil, a PDE5 inhibitor, has been found to cause back pain through its effect on PD11A1. Alteration in the quality of sperm of some patients taking tadalafil has also been reported, supporting the proposal that PDE11A3 inhibition may cause fertility problems[6].

PDE 4 pharmacology with respect to airway inflammation

PDE4s are cAMP specific degrading enzymes. In the lung, cAMP regulates the activity of inflammatory cells and mediates bronchodilation via activation of PKA[7] (Fig. 4). *In vitro,* PDE4 inhibitors suppress NADPH oxidase, degranulation, IgE production, proliferation, and histamine release and cytokines[8]. There is strong evidence that PDE4 inhibitors (e.g. rolipram, cilomilast, and roflumilast) inhibit bronchospasm and improve pulmonary circulation, reduce airway inflammation and remodeling[9], reduce COPD exacerbations and improve patient quality of life[10].

T lymphocytes

Several cAMP inducers, such as PDE4 inhibitors, β2-agonists, cAMP analogs and prostaglandins, were shown to induce the IL-4 directed IgE production; however, one study has shown that IL-4 induced IgE production can be potentiated by cAMP only when B cells are stimulated at a suboptimal concentration of IL-4[5].

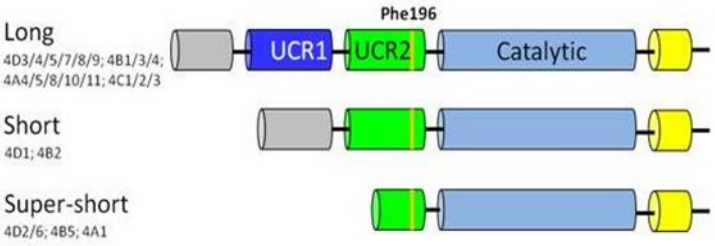


Fig 3. PDE4 structure [4]

Monocytes and macrophages

It has been shown that TNF-α and granulocyte-macrophage colony stimulating factor (GM-CSF) can be suppressed via PDE4 inhibition. LPS stimulation of macrophages induces a large increase in TNF-α mRNA by increasing gene transcription through the activation of the NF-κB and the Jun/Fos -mediated transcriptional regulation. This was shown to be markedly inhibited by rolipram (PDE4 inhibitor) in blood monocytes more than in tissue macrophages, indicating that PDE4 is essential for LPS-activated TNF-α responses. One study has demonstrated that PDE4B but not PDE4D ablation is associated with the prevention of LPS-stimulated TNF-α mRNA and protein accumulation. PDE4B gene expression is selectively induced by LPS, with PDE4B2 being up-regulated[5].

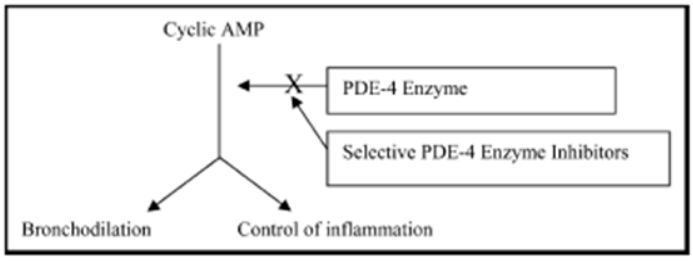


Fig 4. The role of PDE-4 and selective inhibitors[7]

Neutrophils

PDE4 inhibition reduces a variety of neutrophil responses, including N-formyl-methionyl-leucyl-phenylalanine (fMLP) -induced generation of superoxide anion and LTB4, degranulation, and expression of adhesion molecules. Ariga and colleagues[12] reported that ablation of PDE4B and PDE4D but not PDE4A, markedly decreased neutrophil migration to the lung and CD18 (adhesion molecule) expres-

sion in the neutrophils after LPS inhalation. Moreover, chemotaxis induced by IL-8 or macrophage inflammatory protein (MIP)-2 is also attenuated in the splenic neutrophils of PDE4B and PDE4D null mice.

Eosinophils

PAF (platelet-activating factor) and C5a-stimulated LTC4 synthesis in eosinophils has been shown to be suppressed by PDE4 inhibitors. This LTC4 suppression was reversed by the protein kinase A inhibitor Rp-8-Br-cyclic AMPS indicating that it is mediated via PKA activation by cAMP. Moreover, theophylline and rolipram suppress the mobilization of arachidonic acid, which is important for LTC4 derivation, resulting in LTC4 inhibition[13].

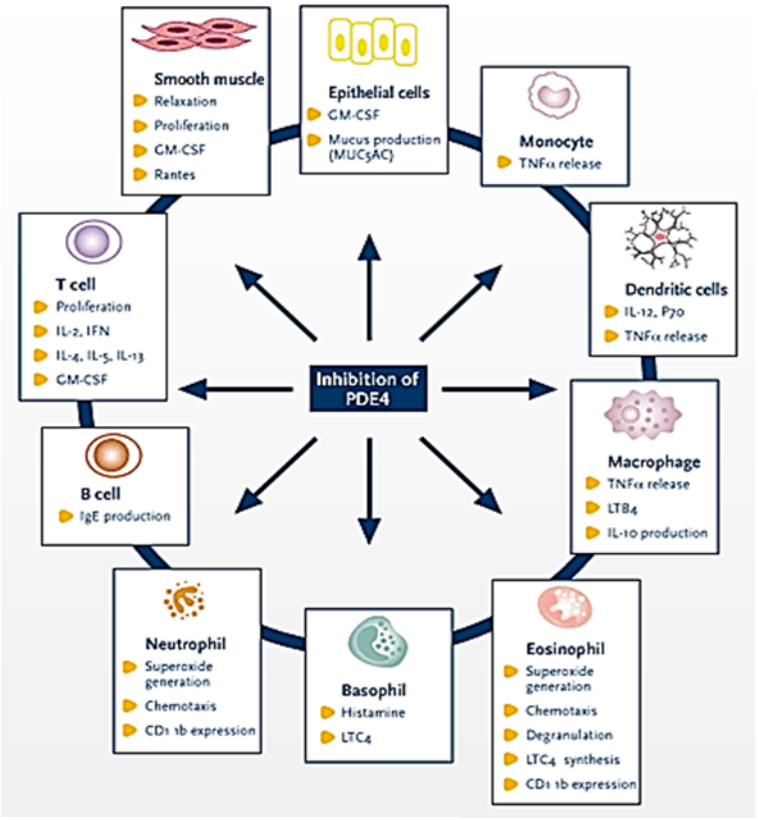


Fig 5. Effects of PDE4 inhibition [8]

These critical findings support therapeutic use of PDE4 (in particular PDE4B) inhibitors in airway diseases as a promising approach with less side effects.

Airway inflammation in COPD

COPD is characterized by poorly reversible airway limitation and associated with cellular and structural changes in both peripheral and central airways. Structural changes include mucus metaplasia, bronchiolar smooth-muscle hypertrophy, mural edema, peribronchiolar fibrosis and excess mucus production[14].

The inflammatory response involves both the innate and acquired immune system[15]. Macrophage number is known to be elevated in bronchial submucosa, bronchial glands and small airways epithelium[14]. After alveolar macrophage induction, they release TNF-α, IL-6, IL-8, IL-1, and leukotriene B4 (LTB4), with subsequent up-regulation of vascular adhesion molecule VCAM-1 all of which, in combination, enhance the immune response[15,16]. VCAM-1 mediates adhesion of lymphocytes, monocytes, eosinophils and basophils to the vascular endothelium[15].

IL-8 and TNF-α attract neutrophils from the circulation to the site of inflammation through direct chemotaxis[15]. Sputum from COPD patients contained higher numbers of neutrophils and higher levels of TNF-α and IL-8 compared with smoking and non-smoking control subjects. This increase correlates with disease severity [17]. Once the neutrophils migrate to the site of inflammation, they secrete elastases, cathepsin G and proteinase-3.

All of these proteases are potent stimulants of mucus secretion from submucosal glands and goblet cells in the epithelium. They up-regulate MUC genes causing increased biosynthesis of mucins to replenish the secretory granules, causing sustained mucin secretion[15].

Neutrophil elastases are also capable of degrading all components of the extracellular matrix (ECM), including elastin, fibronectin and collagen, causing elastin destruction and structural damage to tissue and airways[15]. Elastic fiber destruction decreases the recoil of lungs during exhalation and leads to air trapping[15]. A correlation between neutrophil infiltration and both air trapping and severity of airflow obstruction has been confirmed[16] (Fig.6).

Macrophages also secrete two matrix metalloproteinases (MMPs), neutrophil collagenase (MMP8), and gelatinase B (MMP9) which, in combination, can degrade most components of ECM. MMPs synthesis and secretion is strictly regulated by cytokines, endotoxin, phagocytosis and growth factors, whereas, neutrophil proteinases are rapidly released from the storage granules upon activation[18]. Cultured macrophages taken from COPD patients showed increased amounts of MMP-1 and MMP-9, and *in vivo* increased immunoreactivity for MMP-2 and MMP-9[16]. Recent evidence shows that MMP-12 also has a role in neutrophil influx into the lungs through TNF-α

release, with subsequent up-regulation of VCAM-1[19].

Total T cell number including CD4+ and CD8+ has been reported to be increased in the alveolar walls in bronchial biopsy specimens of COPD patients. T lymphocyte CD4/CD8 ratio was shown to be shifted in favor of the CD8. Sputum taken from COPD patients showed higher CD8+ levels and perforin expression and increased cytotoxic activity, than those taken from control subjects[16,20]. A relationship between apoptosing cell and CD8+ T cell numbers in the alveolar walls has been observed indicating that CD8+ cells induce structural cell apoptosis[21] supporting systemic inflammation involvement in COPD[14].

Theophylline effectiveness and limitations in COPD

Theophylline, a weak and non-selective PDE inhibitor, has been used in COPD treatment for more than 70 years; however, the frequency of its side effects and relatively low efficacy has led to a reduction in its usage. It tends to be a third line agent, added to inhaled bronchodilators for patients with more severe disease. There is no evidence of any theophylline selectivity for PDE4 which is predominant in inflammatory cells, or PDE3 predominant in airway smooth muscle. This non-selectivity may account for nausea and headaches as theophylline plasma concentrations increase[22].

Bronchodilation effect

Bronchodilation is more likely due to PDE inhibition. PDE3 and PDE4 inhibition results in cAMP increase and PDE5 inhibition in cGMP increase. cAMP activates PKA which in turn phosphorylates several target proteins leading to an increase in Ca-activated K channel sensitivity. The opening of Ca-activated K channels allows K^+ efflux, resulting in hyperpolarisation and decreased cell excitability[32]. Charybdotoxin, a Ca-activated K channel blocker, was shown to reduce theophylline bronchodilator effect, suggesting that theophylline opens these channels via cAMP increase. cGMP, on the other hand, can act with the help of nitric oxide to stimulate a cGMP-dependent protein kinase that activates myosin light chain phosphatase, leading to relaxation. Relatively high concentrations of theophylline are needed for maximal relaxation of airway smooth muscles through PDE inhibition. The therapeutic range of theophylline in plasma was established at 10-20 mg/L[22].

Rossi *et al*[24] performed a comparative study between 12 µg (F12) or 24 µg (F24) inhaled formoterol twice daily via a single-dose, and oral slow-release theophylline dose that targets plasma levels between 8 and 20 mg/L at 3-4 h after the morning dose. The results showed that formoterol is superior to oral slow-release theophylline in terms of bronchodilator effect magnitude (AUC-FEV1, over 12 h) and prevention of mild COPD exacerbations.

Anti-inflammatory effect

Low doses of theophylline were shown to reduce the number and proportion of neutrophils in induced sputum, IL-8 concentration, myeloperoxidase and neutrophil chemotactic responses in COPD patients. These anti-inflammatory effects are seen at concentrations less than 10 mg/L, which is below the dose at which bronchodilation is achieved. IL-10 is increased by theophylline due to PDE inhibition[22]. Theophylline was shown to reduce the expression of inflammatory genes in asthma and COPD by preventing the translocation of the pro-inflammatory transcription factor NF-κB into the nucleus. However, these effects appear at high concentrations and may be mediated by PDE inhibition[22].

Theophylline suppresses the expression of granulocyte-macrophage–colony stimulating factor (GM-CSF) and IL-8 through histone deacetylase (HDAC) activation. This effect is seen at therapeutic concentrations (10^{-5}-10^{-6} M) but lost at higher concentrations (10^{-4} M), and reversed by the non-selective HDAC inhibitor trichostatin A. Bronchial biopsies taken from patients treated with low doses of theophylline (mean plasma concentration~5 mg/L) showed a significant increase in HDAC activity, indicating that low concentrations are sufficient to activate HDAC *in vivo*[24].

HDACs are effective in switching off the inflammatory genes only when they are recruited to the active inflammatory site by active glucocorticoid receptors. Theophylline was shown to reverse the effect of oxidative stress and cigarette smoke extract through direct activation of HDACs, and thus restore corticosteroid responsiveness in cell lines and alveolar macrophages from smokers and patients with COPD[22].

Side effects

Theophylline has a narrow therapeutic margin with many side effects, and a tendency to interact adversely with other drugs through competition with various cytochrome (CYP) 450 enzymes. Unwanted effects are dose dependent and tend to occur when plasma levels exceed 20 mg/L. The most common ones are headache, nausea and vomiting, abdominal discomfort, restlessness, increased acid secretion, gastroesophageal reflux and diuresis. At high concentrations, convulsions, cardiac arrhythmias and death may occur. Caffeine intake should be limited when taking theophylline[22].

Theophylline is a potent inhibitor of adenosine receptors at therapeutic concentrations, and this may be beneficial for asthmatic patients but its significance to COPD patients is not well known yet. However, adenosine antagonism is likely to account for seizures and cardiac arrhythmias through blockade of A1 receptors. Use of low doses (plasma concentrations of 5-10 mg/L) largely avoids side effects and drug interactions, and makes it unnecessary to monitor plasma concentrations[22].

Although theophylline appears to improve FEV1 and FVC and reduces pulmonary vascular resistance in patients with clinically stable COPD, its benefits have to be weighed against its adverse effects. It is used as an add-on treatment for patients not adequately controlled with inhaled bronchodilators. Long-term treatment with inhaled long-acting β_2 agonists (LABA) dry powder was shown to be more effective and better tolerated [24].

Roflumilast and COPD pharmacotherapy

Cilomilast and roflumilast are examples of selective PDE4 inhibitors that have the potential to improve theophylline's beneficial effects and reduce its adverse effects. Cilomilast development has been terminated because of its untolerated GIT side effects such as emesis due to its PDE4D selectivity. Roflumilast in turn inhibits most PDE4 isoenzymes with a slightly lower potency against PDE4C[25].

In 2010, roflumilast was approved by the European Medicines Agency Committee for Medicinal Products for Human Use, for the maintenance treatment of severe COPD (FEV1 postbronchodilator <50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations, as an add-on to bronchodilator treatment[25].

Pharmacodynamics of roflumilast

Preclinical data

Preclinical studies have shown that roflumilast improves lung function and significantly decreases pulmonary inflammation. In an acute mouse model of smoking (five cigarettes for 20 min), roflumilast was administered orally at a dose of 1 or 5 mg/kg, and bronchoalveolar lavage fluid (BALF) changes were investigated at 4 and 24 h after cigarette smoke exposure. In the chronic model (three cigarettes/day for 7 months), morphometric and biochemical parameters were assessed. Acute exposure caused a fivefold increase in BALF neutrophils and the results showed that both roflumilast doses attenuated this increase by approximately 30% and increased IL-10 levels. Chronic exposure caused a 1.8-fold increase in lung macrophage number and emphysema, as well as a decrease in the internal surface area and a drop in lung desmosine content, an elastin specific imino-acid. The 1mg/kg dose did not have any effect in the chronic smoke exposure model, whereas the 5mg/kg dose decreased the elevation in lung macrophage number by 70% and completely prevented other pulmonary changes[26].

Clinical findings

Anti-inflammatory effects

In a double-blind, crossover study of 38 patients with COPD receiving 500 µg roflumilast once daily or placebo, induced sputum samples were collected before and after 4 weeks of treatment. The absolute number of neutrophils and eosinophils/g sputum was reported to be reduced in the roflumilast group by 35.5% and 50%, respectively, compared with placebo[27] (Fig. 7).

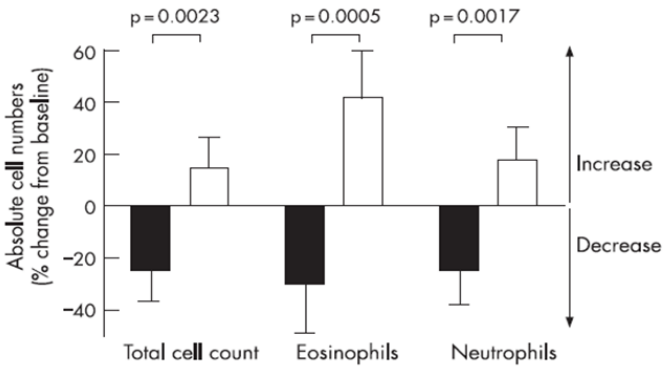


Fig.7. Change in total cell count and numbers of neutrophils and eosinophils in sputum during roflumilast (black bars) and placebo (white bars) treatment for 4 weeks[27]

The soluble markers of neutrophilic and eosinophilic inflammatory activity were significantly re-

duced. IL-8 was reduced by 26%, neutrophil elastase (NE) by 31% and eosinophil cationic protein (ECP) by 34%, as well as a 41% reduction in α2-Macroglobulin, a microvascular leakage marker (Fig. 8). The number of macrophages and lymphocytes was also shown to be reduced by 24 and 35%, respectively, meaning that the anti-inflammatory effect of roflumilast may account for its clinical efficacy, rather than a reduction in airway smooth muscle tone[27].

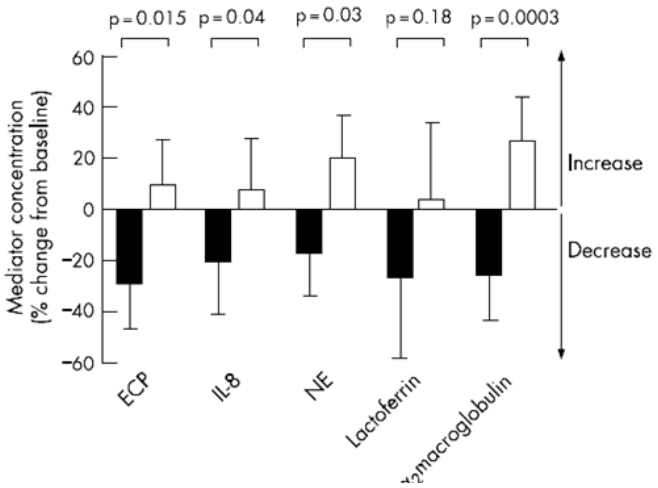


Fig 8. Changes in ECP, IL-8 and NE, lactoferrin and α2-macroglobulin levels in sputum supernatants during roflumilast (black bars) and placebo (white bars) treatment for 4 weeks[27]

Effects on lung function & quality of life

All clinical trials have reported statistically significant improvements in FEV1, ranging from 36-88 mL, when roflumilast treatment was compared with placebo.

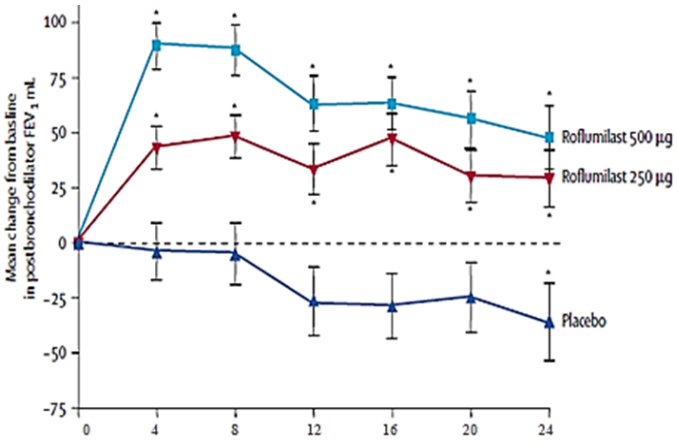
Rabe and colleagues[28] evaluated 250 and 500 µg roflumilast once daily versus placebo in a double-blind, randomized study of 1411 patients with moderate to severe COPD (age ≥40 years; COPD for ≥ 12 months) and with a post-bronchodilator FEV1 of 30-80% predicted value and a post-bronchodilator FEV1:FVC ratio of 0.70 or less. They were randomly assigned roflumilast 250 µg (n=576), roflumilast 500 µg (n=555), or placebo (n=280) given orally once daily for 24 weeks.

The primary efficacy endpoints in this trial were post-bronchodilator FEV1 and health-related quality of life as measured by the St George's Respiratory Questionnaire (SGRQ). Postbronchodilator FEV1 was increased from baseline in both roflumilast dose groups versus a decline in the placebo. At the 4th week, the improvements in FEV1 were 74 (250µg dose) and 97 ml (500µg dose) respectively (Fig 9). Changes in pulmonary function tests indicate that roflumilast has a dose-dependent response. There was also improvement in health-related quality of life by both doses of roflumilast compared with placebo[28].

Long-term outcomes of roflumilast effectiveness were evaluated by Fabbri and co-workers[29] in a randomized, double-blind study of 1513 patients with COPD, given 500µg roflumilast once daily, compared with placebo for one year. Patient inclusion criteria for this trial were similar to those of the Rabe *et al*[28] trial (24-weeks), but they were required to have an FEV1 of 50% or less predicted and the efficacy endpoints were change in postbronchodilator FEV1 and number of exacerbations. Patients on placebo had a decline in FEV1, whereas FEV1 increased by 39 ml in the roflumilast group.

The effect of roflumilast on lung function in patients with moderate to severe COPD who are already being treated with salmeterol or tiotropium was evaluated in the Fabbri *et al*[29] trial. The pre-bronchodilator FEV1 increased significantly in both arms that used roflumilast, and similar improvements in post-bronchodilator FEV1 and in pre- and post- bronchodilator FVC were reported. Change in post-bronchodilator FEV1 was 68ml improvement in the roflumilast plus salmeterol group, compared with 8ml improvement with salmeterol alone. Post-

Fig 9. Time-dependent change from baseline in postbronchodilator FEV1[28]



bronchodilator FEV1 improved by 74ml in patients receiving tiotropium plus roflumilast, and by 7ml in patients receiving tiotropium alone.

However, the use of short-acting β2 agonists at baseline was reported to be higher in the tiotropium plus roflumilast trial than in the salmeterol plus roflumilast trial indicating that the administration of roflumilast with salmeterol resulted in the best outcomes and the most significant improvements[29].

Rate of exacerbations

Reductions in exacerbations rate have been inconsistent in roflumilast trials in three trials in patients with severe to very severe COPD. Fabbri *et al* [30] reported no significant reduction in the frequency of moderate-to-severe exacerbations (requiring hospitalization) but a significant reduction in the frequency of moderate exacerbations versus placebo. Roflumilast did not significantly reduce the rate of exacerbations above that of LABA; however, this may not reflect the lack of roflumilast effect on exacerbation rate but may be rather due to the fact that patients were optimally controlled on LABA. Median exacerbation rate in patients on salmeterol and salmeterol plus roflumilast was 2.4 and 1.9 respectively. In patients on tiotropium and tiotropium plus roflumilast, it was 2.2 and 1.9, respectively [29].

Tolerability

Adverse effects included diarrhea (8–9%), weight loss (6–12%) and nausea (5%). They were reported to occur more often in COPD patients receiving 500 µg roflumilast. Insomnia, anxiety and depression were also reported. Although there are no well -controlled studies conducted in pregnant women, roflumilast is considered a pregnancy category C drug. Roflumilast and its metabolites have been reported in the milk of lactating rats and this may also occur in humans[30].

Conclusions

Most of the current COPD treatments aim to reduce clinical symptoms rather than targeting COPD pathophysiology. *In vitro* and *in vivo* data support the use of PDE inhibitors in treating COPD due to their action on inflammatory cells such as neutrophils. Their anti-inflammatory and bronchorelaxation effects may be limited by their dose-dependent side effects. Theophylline, a non-selective PDE inhibitor is used clinically but requires careful titration and routine plasma monitoring due to the risk of serious cardiovascular and CNS side effects. Roflumilast, a selective PDE4 inhibitor, was shown to be more convenient to use despite the common adverse events such as nausea, diarrhea and headache. Further studies are needed to evaluate its long-term safety and efficacy. The discovery of more selective PDE4 inhibitors and their administration by inhalation may overcome these limitations.

References

1. Bender AT, Beavo JA. Pharmacol Rev 58:488-520; 2006
2. Lugnier C. Pharmacol Therapeutics 109:36-398; 2006
3. Omori K, Kotera J. Circ Res 100:309–327;2007
4. Keravis T, Lugnier, C. Br J Pharmacol 165:1288-1305; 2012
5. Jin SL, Ding SL, Lin SC. Chang Gung Med J. 35: 197–210;2012
6. Pomara G, Morelli G. Int J Impot Res 17:385–6; 2005
7. Soto FJ, Hanania NA. Curr Opin Pulm Med 11:129-34; 2005
8. Giembycz MA. Proc Am Thorac Soc. 2:326–33 discussion 340–1;2005
9. Holbrook M, Gozzard N, James T et al. Br J Pharmacol 118:1192–200;1996
10. Rabe KF, Bateman ED, O'Donnell D, et al. Lancet 366 (9485): 563–71;2005
11. Peter D, Jin SL, Conti M, Hatzelmann A, Zitt C. J Immunol 178(8):4820-31;2007
12. Ariga M, Neitzert B, Nakae S, Mottin G, Bertrand C, Pruniaux MP, Jin SL, Conti M. J Immunol 173:7531-8; 2004
13. Tenor H, Hatzelmann A, Church MK, Schudt C, Shute JK. Br J Pharmacol 118:1727-35;1996
14. Wouters EF. Proc Am Thorac Soc 2(1):26-33;2005
15. Barnes PJ. Pharmacol Rev 56(4):515-48;2004
16. O'Donnell R, Breen D, Wilson S, Djukanovic R. Thorax 61:448-454;2006
17. Keatings VM, Collins PD, Scott DM, Barnes PJ. Am J Respir Crit Care Med. 153(2):530–534;1996
18. Tetley TD. Curr Drug Targets Inflamm Allergy 4(6):607-18;2005
19. Churg A, Wang RD, Tai H, et al. Am J Respir Crit Care Med 167:1083–9;2003
20. Yokohori N, Aoshiba K, Nagai A. Chest 125:626–32; 2004
21. Majo J, Ghezzo H, Cosio MG. Eur Respir J 17:946–53; 2001
22. Barnes P J. Am J Respir Crit Care Med 167:813–818; 2003
23. Miller C. Genome Biol. 1:reviews0004–reviews 0004. 5; 2000
24. Rossi A, Kristufek P, Levine BE, et al. Chest. 121:1058–69;2002
25. M. A. Giembycz and S. K. Field. Drug Design, Development and Therapy, vol. 4, pp. 147–158, 2010
26. Martorana PA, Beume R, Lucattelli M, Wollin L, Lungarella G. Am. J. Respir. Crit. Care Med. 172(7), 848-853; 2005
27. Grootendorst DC, Gauw SA, Verhoosel RM, et al. Thorax. 62(12):1081–1087;2007
28. Rabe KF, Bateman ED, O'Donnell D, et al. Lancet. 366 (9485):563–571;2005
29. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, et al. Lancet 374(9691):695–703;2009
30. Baye J. P T. 13(3):149–161; 2012

Ashwaq Al Otaibi
Final Year BPharm student
Faculty of Pharmacy, Kuwait University

TEST YOUR KNOWLEDGE

Answers on back page

1. Which of the following is a selective PDE4 inhibitor used for the maintenance of severe COPD?

A. roflumilast
B. salbtamol
C. ipratorpium
D. mollelast
E. beclomathasone

2. *Which of the following was shown to induce the IL-4 directed IgE production?*

A. PDE4 inhibitors
B. β2-agonists
C. cAMP analogs
D. prostaglandins
E. all of the above

3. *Which of the following is not a common side effect of theophylline?*

A. headache
B. nausea
C. seizures
D. restlessness
E. gastroesophageal reflux

Is there a problem?

A 10 year old patient was given the following prescription for fever. Is there any major error in the prescription?

BMX HOSPITAL

Patient Name: Ali Mohammad Age: 10 years
Address: Street No.21

Rx

Aspirin tablet
300 mg every 4 hours
Send one pack

Dr. Ahmad
Signature Date: 5/12/14

Answer (Prescription Exercise)

Aspirin is not recommended for children < 16 years due to possibility of developing Reye's syndrome.

Source:
British National Formulary

TOPICAL ISSUES AND CONTROVERSIES

Antibiotic cycling could help clinicians battle simultaneously both illness and resistance

The employment of a treatment framework in which clinicians administer different drugs in strategic succession could both treat bacterial infections and select against the development of resistance.

This new framework, which the researchers call collateral sensitivity cycling, could also help curb unnecessary antibiotic use, which is known to contribute to the emergence of drug-resistant superbugs. The idea of alternating antibiotics to both beat bacterial infections and outsmart pathogens on the path to acquiring resistance has circulated in the minds of microbiologists for decades, but clinical data to date have been unconvincing.

According to researchers, the thought behind traditional drug cycling is that if you alternate between drugs, you alternate between selection pressures, so if you don't have the selection pressure for resistance, then resistance will disappear. Although this type of traditional drug cycling has at times been shown to be advantageous, at other times it has shown to have no effect at all.

For the present study, both wild-type Escherichia coli and strains evolved in the laboratory to be re-

sistant to 23 commonly used antibiotics were analyzed. The researchers performed dose-response experiments to determine the susceptibility of each isolate to a variety of compounds. They then treated those strains with pairs of drugs in a cyclical fashion, such that as the bacteria began to develop resistance to drug A- as measured by the amount of drug it took to inhibit bacterial growth- the team quickly switched to drug B. Later, as the bacteria began to develop resistance to drug B, the researchers applied drug A once more.

The work identified several such sets of antibiotics for which such cycling successfully killed the bacteria without allowing resistance to take hold. Interestingly, they found that drugs belonging to a specific class do not always induce the same effects among the bacteria. As such, the researchers noted that the specific drugs E. coli is exposed to may play a role in determining its sensitivity profile.

This study is an in-depth analysis of resistance linkages and susceptibilities and it's an important topic because development of antimicrobial drugs is expensive and time-consuming, and there aren't very many in the pipeline, so other ways to control resistance are very important. Still, even if cycling were to improve treatment outcomes, some scientists wonder whether switching up antibiotics can actually help stave off drug resistance in the clinic, or if doing so might contribute to a bigger problem. If the cycling results in an overall reduction in antibiotic usage, resistance rates can go down. But if the cycling results in a reduction in usage of a specific antibiotic as it is replaced by another antibiotic, all that is achieved is replacement of resistance for one drug with another and as soon as the drug that is stopped cycles back on, the resistance comes right back as evidenced by previous clinical data.

Some experts are not convinced that *in vitro* test results are enough to support clinical use of collateral sensitivity cycling at this point and that extensive validation studies are needed. They also added that coming to understand the mechanisms that govern collateral sensitivity will be key. It's important to figure out what makes certain bacteria highly sensitive to some drugs while particularly resistant to others.

1. L. Imamovic, M.O.A. Sommer, "Use of collateral sensitivity networks to design drug cycling protocols that avoid resistance development," Science Translational Medicine, doi: 10.1126/scitranslmed.3006609, 2013.
2.http://www.the-scientist.com/?articles.view/articleNo/37629/title/Giving-Antibiotic-Cycling-Another-Shot/

Acetaminophen use during pregnancy linked to ADHD risk in kids

Children whose mothers used acetaminophen during pregnancy had an increased risk for behavioral problems related to ADHD, but experts advise that more research is required to investigate the association.

Although acetaminophen is considered safe for use by pregnant women, new research suggests that fetal exposure to the medication may increase the risk for behavioral problems related to attention-deficit/ hyperactivity disorder (ADHD) in children.

Previous research has suggested that acetaminophen has endocrine-disrupting properties that could affect fetal brain development. To investigate the nature of these potential effects, a study, published on *February 24, 2014, in JAMA Pediatrics,* assessed the association between maternal use of acetaminophen during pregnancy and the risk for developing ADHD-like behaviors, being diagnosed with hyperkinetic disorders (HKDs), or using ADHD medications in children who were enrolled in the Danish National Birth Cohort from 1996-2002.

Mothers reported their use of acetaminophen in 2 telephone interviews during pregnancy and an additional interview 6 months after giving birth. When a participating child reached age 7y, the child's mother or another caregiver completed the Strengths and Difficulties Questionnaire to assess ADHD-like behaviors. Children who were diagnosed with an HKD at age 5 y or older and those who filled 2 or more prescriptions for ADHD medications were identified through national registries.

More than half (56%) of all women included in the study reported using acetaminophen during pregnancy. The results indicated that children who were exposed to acetaminophen while in the womb were at increased risk of being diagnosed with an HKD (hazard ratio 1.37), using ADHD medications (hazard ratio 1.29), or having ADHD-like behaviors at age 7 (risk ratio 1.13) compared with those who had not been exposed to the medication.

These risks were even greater when women increased their use of the medication throughout their pregnancy or when they reported taking it in more than 1 trimester. When women reported using acetaminophen for 20 or more weeks during pregnancy, the risk of HKD diagnosis in children nearly doubled (hazard ratio 1.84) and the risk for taking ADHD medications increased by 50%. The relationship between prenatal acetaminophen exposure and risk for all outcomes did not change when possible confounders, including maternal inflammation and infection during pregnancy and maternal mental health problems, were accounted for.

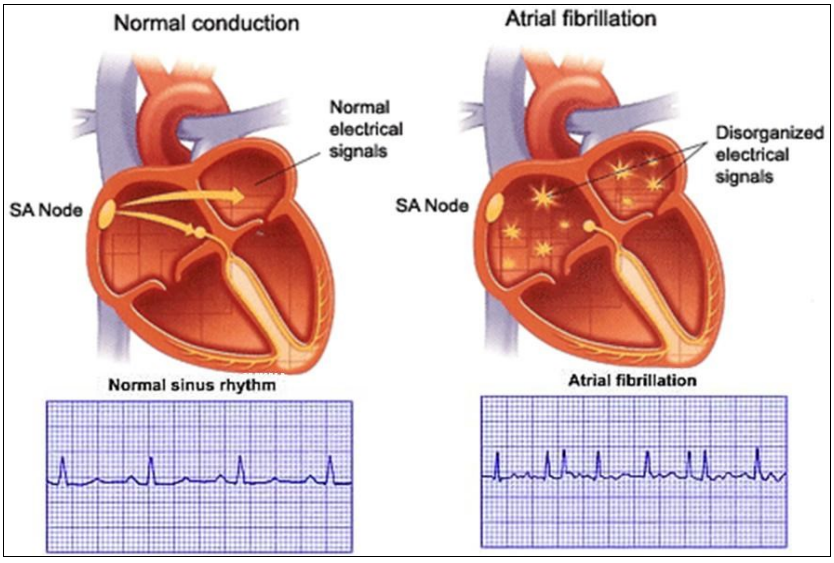
Although the study's results may seem alarming, the findings do not prove a cause-and-effect relationship and should be interpreted with caution. Considering the common use of acetaminophen during pregnancy and the large number of children diagnosed with ADHD, additional studies are needed to expand on the evidence and further investigate the association. These findings underline the importance of not taking any drug's safety during pregnancy for granted.

Source:
http://www.pharmacytimes.com/news/Acetaminophen-Use-During-Pregnancy-Linked-to-ADHD-Risk-in-Kids?utm_source=twitterfeed&utm_medium=twitter

Antibiotics linked with increased arrhythmia, death risks

Short-term treatment with the antibiotics azithromycin and levofloxacin may increase the risk of serious cardiac arrhythmias and death, the results of a new study indicate.

Previous findings have suggested a relationship between treatment with azithromycin and an increased risk of cardiovascular death and all-cause mortality in US Medicaid patients, especially those at a high risk for cardiovascular disease. These findings led the FDA to issue a public safety warning about the potential risks associated with the antibiotic and similar risks linked with levofloxacin.



http://www.rwjuh.edu/news/new_atrial_fibrillation.html

Expanding on this research, the current study, published in the *March/April 2014 issue of the Annals of Family Medicine*, analysed data from a cohort of veterans treated with azithromycin, levofloxacin, or amoxicillin and evaluated the risks of cardiac arrhythmia and death associated with use of each antibiotic. The analysis included 14 million patients who were treated at 140 Department of Veterans Affairs Medical Centers and 600 outpatient clinics from September 1999 through April 2012. Azithromycin was typically dispensed for 5 days, while amoxicillin and levofloxacin were generally dispensed for 10 days.

The results indicated that treatment with either azithromycin or levofloxacin was associated with a significant increase in the risk of death and serious arrhythmia. Based on weighted analysis, 228 patients treated with azithromycin and 384 of those treated with levofloxacin per million antibiotics dispensed died after 5 days of treatment, compared with just 154 deaths in patients treated with amoxicillin. At 10 days after the start of treatment, 422 azithromycin patients and 714 levofloxacin patients died per

million antibiotics dispensed, compared with 324 amoxicillin patients. Within the first 5 days of treatment, patients receiving azithromycin had a 48% increased risk of death and a 77% increased risk of serious arrhythmia compared with patients who took amoxicillin. During days 6 to 10 after the beginning of treatment, however, the risk of both death and serious arrhythmia in patients receiving azithromycin were not significantly increased compared with those taking amoxicillin.

During the first 5 days of treatment, patients who received levofloxacin had a 149% increased risk of death and 143% increased risk of serious arrhythmia compared with those who took amoxicillin. The increased risks associated with taking levofloxacin compared with taking amoxicillin remained significantly increased throughout the 10-day treatment period, with the risk of death increased 95% and the risk of serious arrhythmia increased 75%.

The findings support safety announcements from the manufacturer of azithromycin and the FDA, the authors note. They suggest that providers should consider the risks and benefits of the antibiotics before making prescribing decisions.

Adapted from http://www.pharmacytimes.com/news/Antibiotics-Linked-with-Increased-Arrhythmia-Death-Risks#sthash.Q2RugjLA.dpuf

Survey suggests that US prescription drug use may be widespread

Nearly 70% of the people in Olmsted County, Minnesota, US, are taking at least a single prescription drug and more than half are taking 2, according to results from a new survey. The findings could suggest patterns in the United States as a whole, and the use of antidepressants and opioid analgesics warrants further study.

According to experts, often when people talk about health conditions they're talking about chronic conditions such as heart disease or diabetes, however, the second most common prescription was for antidepressants — that suggests mental health is a huge issue and is something to be focused on. And the third most common drugs were opioids, which is a bit concerning considering their addicting nature.

The study was conducted at the Mayo Clinic and the nearby Olmsted Medical Center, both of which are in Rochester, Minnesota, US. The researchers presented their results in an article published online on *June 21 in Mayo Clinic Proceedings*. They based their findings on the 2009 medical records of 142,377 people, which they estimated to be 98.7% of the people living in Olmsted County, Minnesota. They found that 68.1% of the population received a prescription from at least a single drug group, 51.6% received a prescription from 2 or more drug groups, and 21.2% received prescriptions from 5 or more drug groups.

The researchers found that 17% of the population was receiving penicillins and b-lactam antimicrobials, making this the largest drug group. The next largest group was antidepressants, which were being taken by 13% of the population. The third largest was opioid analgesics, at 12%, followed by antilipemic agents at 11%. Women and girls received more prescriptions than men and boys in almost every category.

Among the biggest differences by sex were antidepressants, with 16.21% of women receiving these prescriptions compared to 8.56% of men and boys. Men and boys received more antilipemic agents, beta-blockers, and angiotensin-converting-enzyme inhibitors.

Overall, prescriptions increased with age, especially those for antidepressants, opioid analgesics, gas-

trointestinal medications, laxatives, and cardiovascular disease drugs. Vaccine/toxoids, penicillin and beta-lactam antimicrobial prescriptions were most prevalent in children, however; they were least prevalent in young adults. Antiasthmatics, topical anti-infective / anti-inflammatory agents, erythromycins/macrolides, topical nasal and throat agents, and antihistamines were relatively stable by age group.

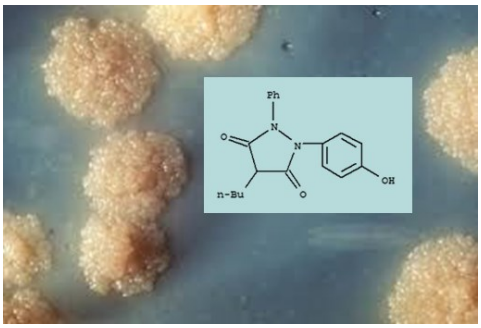
The researchers were surprised to discover opioid analgesics were prescribed in all age groups, including young adults, but said the explanation is that their findings included prescriptions for acute pain as well as chronic pain.

In general, the discoveries about the Olmsted County population were consistent with what is known about the US population as a whole. However, the National Health and Nutrition Examination Survey reported a 48% monthly use of one or more prescription drugs in 2007 to 2008. The authors concluded that the findings are useful for understanding the prescribing patterns across all ages in a defined population and important baseline information for future studies of drug-related adverse events, drug-drug interactions, polypharmacy, health-seeking behaviors, and other prescription-related aspects of health care utilization.

Source: http://www.medscape.com/viewarticle/806757

IN THE NEWS

Double-edged TB drug



An inexpensive, over-the-counter pain reliever can kill the bacteria that cause tuberculosis (TB)- even the drug-resistant varieties- according to a study published online in the *Proceedings of the National Academy of Science, September 10, 2012)*, yet it's not a promising candidate for drug trials.

Researchers at the Weill Cornell Medical College designed a screen to find drugs that target dormant TB bacteria- triggered by certain lung conditions, dormancy is a key strategy *Mycobacterium tuberculosis* uses to evade drugs and cause lethal infections in nearly 1.5 billion people per year. The researchers found that the anti-inflammatory drug oxyphenbutazone, developed to treat arthritis in the 1970s, is activated in lung conditions that induce dormancy, and can kill dormant, active, and even resistant bacteria.

But the researchers are skeptical the drug will ever be given to a TB patient. No drug firm will pay for clinical trials if they don't expect to make a profit on the agent. And that would be the case for an off-patent drug that people can buy over the counter for pain in most of the world.

Another hurdle for the drug is that it can't be tested in mouse models because the animals metabolize the drug to an inactive form faster than humans do- too fast to treat TB infection.

This makes testing the drug for TB use in humans problematic since the FDA requires pre-clinical animal testing studies for safety and efficacy although there is a long track record of oxyphenbutazone's relatively safe use in hundreds of thousands of people over decades.

FDA Approvals

Hurry up FDA -Faster approval of new devices

Along with medical device companies and non-profit organizations, the US FDA is taking part in a new public-private partnership, called the Medical Device Innovation Consortium (MDIC), which aims to develop better tools for evaluating medical technologies, and do so more quickly.

The path to developing new medical devices for clinical use in the US is a lengthy one. Unlike in Europe, where companies only have to show that a device is

safe, in the US they must also demonstrate a device's clinical effectiveness in treating a disease or medical condition. This has led to an *approval lag* in which devices typically reach US patients only after they have been on the market in the EU for several years.

To shorten that time lag, the FDA is now looking to industry for ideas - which is where the consortium comes in. By sharing resources between MDIC members, for example, the FDA hopes to create effective, efficient and standardized ways to validate and review devices and to prioritize funding and regulatory science decisions. Experts believe that this is the first time that one can determine priorities, bring together collaborative minds and analyze post-market values to determine safety and efficacy. The FDA also hopes that the MDIC will help speed this process by allowing consortium members to share resources and prioritize time and money.

Meanwhile, the regulatory agency is also feeling pressure from the drug industry to accelerate approvals of new antibiotics, to help thwart the rising problem of antibiotic resistance. Specifically in question is a new vancomycin derivative known as telavancin (Vibativ), which has shown signs of efficacy in treating hospital-acquired pneumonia when other drugs have failed or are not suitable. But in the summer of 2010, the FDA rejected the drug -for a second time- citing a lack of robust clinical data.

Later on at a meeting in Maryland, FDA advisers recommended telavancin's approval, which some see as a sign that the agency may be relaxing its ultra-strict approval criteria for antibiotics. However it remains unclear about what the ultimate fate of telavancin will be. The vote follows a pledge by Janet Woodcock, head of the FDA's Center for Drug Evaluation and Research, to "reboot" antibiotic-approval process, as well as the passage of a set of rules by Congress aiming to speed antibiotic development.

Sources:

1) http://www.the-scientist.com/?articles.view/articleNo/33564/title/Hurry-Up--FDA/

2) http://blogs.nature.com/spoonful/2012/12/fda-announces-partnership-to-speed-development-of-new-medical-device-technologies.html

FDA reform to boost US economy?

It has been proposed to replace Phase 3 trials with smaller, faster alternatives and post-market surveillance to invigorate the pharmaceutical industry.

By phasing out Phase 3 trials and thus lowering the barriers facing drug development in the US, the FDA could improve the health of millions and spur economic growth.

Noting the "glacial" pace of the drug approval process, the current output of new drugs could be doubled if the FDA altered its expensive and laborious clinical-trial requirements. Specifically, Phase 3 trials -in which the effectiveness of a candidate drug is assessed in large groups over extended periods of time -is doing more harm than good because it is severely reducing the pharmaceutical industry's incentive to invest in new treatments. Instead, a system is proposed in which a new drug could come to market after promising early-stage results, and patients and insurers could judge its effectiveness. Drugs could then be improved based on that feedback. And though companies would still be liable for unforeseen side effects, patients and doctors would be warned that the drug was approved based on provisional research.

Phasing out Phase 3 trials would reduce development costs by 25% and ensure revenues started arriving 3 years earlier, resulting in significantly increased profit margins. According some experts, this would double the number of new drugs, increase the health and longevity of patients and boost the US economy.

Also, reducing phase 3 requirements would enable earlier introduction of drugs for chronic diseases such as obesity, but it is the fear of missing rare side effects, so companies would still be required to conduct post-marketing requirements.

Source:

http://www.the-scientist.com/?articles.view/articleNo/34594/title/FDA-Reform-to-Boost-US-Economy-/

STATE OF KUWAIT
Pharmaceutical & Herbal Medicines Control and Registration Administration

New Pharmaceutical products approved from September to December 2014

Amaryl M Tablets 1/500mg; Glimepiride- 1mg Metformin HCl-500mg; Handok Pharm. Co. Ltd./Korea
Aubagio Tablets 14mg; Teriflunomide-14mg; Genzyme Europe B.V. /The Netherlands
Bronclyn Syrup 15mg/5ml; Terbutaline Sulphate-1.5mg; Medpharma Pharm. & Chem. Ind. (LLC)/U.A.E.
Cisatracurium-hameln Soln. for Inj./Infn. 5, 10, 20mg; Cisatracurium-5, 10, 20mg; Hameln Pharma GmbH- Germany
Clairyg Solun. For Infn. 10g/200ml; Human normal IgG (IV IG)-10g; LFB Biomedicaments/ France
Clairyg Solun. For Infn. 1g/20ml; Human normal IgG (IV IG)-1g; LFB Biomedicaments/ France
Clairyg Solun. For Infn. 2.5g/50ml; Human normal IgG(IV IG)-2.5g; LFB Biomedicaments/ France
Clairyg Solun. For Infn. 20g/400ml; Human normal IgG (IV IG)-20g; LFB Biomedicaments/ France
Clairyg Solun. For Infn. 5g/100ml; Human normal IgG(IV IG)-5g; LFB Biomedicaments/ France
Clopivid Tablet 75mg; Clopidogrel-75mg; Hovid BHD-Malaysia
Dexahexal Soln. for Injn. 4mg; Dexamethasone Phosphate-4mg; Hexal AG/Germany
Dexilant Capsules 30, 60mg; Dexilansoprazole-30, 60mg; Takeda Pharm. USA Inc-U.S.A.
Dexketoprofen Normon Granules for Oral Soln. 25mg; Dexketoprofen-25mg; Lab. Normon S.A. /Spain
Edarbi Tablets 40, 80mg; Azilsartan Medoxomil-40, 80mg; Takeda Pharm. USA Inc-U.S.A.
Edarbyclor Tabs. 40/12.5mg; Azilsartan Medoxomil-40mg Chlorthalidone-12.5mg; Takeda Pharm. /USA
Edarbyclor Tabs. 40/25mg; Azilsartan Medoxomil-40mg Chlorthalidone-25mg; Takeda Pharm. /USA
Esomeprazole Normo Pwd. For Inject Soln. for Infn.; Esomeprazole-40mg; Lab. Normon S.A. /Spain
Gazyva Conc. for Soln. for Infn. 1000mg/40ml; Obitunuzumab - 1000mg Histidine-57.6mg; F.H. La Roche Ltd./Switzerland
Giotrif Tablets 20, 30, 40, 50mg; Afatinib-20, 30, 40, 50mg; Boehringer Ingelheim Pharm. GmbH & Co. KG/Germany
Glucose IV Infn. BP; Glucose -5g; Claris Lifesciences Ltd.-India
Hairgaine Topical Soln. 2% for women; Minoxidil-20mg; Medpharma- U.A.E.
Imipenem-Cilastatin Labatec Pwd. For Soln. for Infn. 500/500mg; Imipenem-500mg, Cilastatin-500mg; Labatec Pharma S.A. / Switzerland
Invega Sustenna PR Suspn. 100mg/1ml; Paliperidone-100mg; Janssen-Cilag Intl. B.V.- Belgium
Invega Sustenna PR Suspn. 150mg/1.5ml; Paliperidone-150mg; Janssen-Cilag Intl. B.V.- Belgium
Invega Sustenna PR Suspn. 25mg/0.25ml; Paliperidone-25mg; Janssen-Cilag Intl. B.V.- Belgium
Invega Sustenna PR Suspn. 50mg/0.50ml; Paliperidone-50mg; Janssen-Cilag Intl. B.V.- Belgium
Invega Sustenna PR Suspn. 75mg/0.75ml; Paliperidone-75mg; Janssen-Cilag Intl. B.V.- Belgium
Irokid Syrup 50mg/5ml; Iron-50mg; Medpharma- U.A.E.
Ketorolac Trometamol Normon Injectable Soln. 30mg/ml; Ketorolac Trometamol-30mg; Lab. Normon S.A. /Spain
Lainema Rectal Solution; Sodium Dihydrogen Phosphate-139mg Disodium Hydrogen Phosphate-32mg; Lainco S.A. / Spain
Lastacaft Ophthalmic Soln. 0.25%; Alcaftadine-2.5mg; Allergan Inc./U.S.A.
Levofloxacin Normon Soln. for Infn. 5mg/ml; Levofloxacin -500mg; Lab. Normon S.A. / Spain
Levofloxacin Normon Tablets 500mg; Levofloxacin-500mg; Lab. Normon S.A. /Spain
Loflam Tablets 100mg; Aceclofenac - 100mg; Medpharma- U.A.E.
Maalox Stomach Pain Sugar Free Tablets 400mg; Magnesium Hydroxide- 400mg Aluminium Hydroxide- 400mg; Sanofi-Aventis S.p.A./Italy
Methylprednisolone Normon Pwd. & Solvent for injectable Soln. 40mg/2ml; Methylpredinsolone-40mg; Lab. Normon S.A. / Spain
Mucoangin Mint Lozenges; Ambroxol HCl-20mg; Boehringer Ingelheim Pharm. GmbH. KG/Germany

MultiBic potassium free Soln. for haemofiltration; Sodium Chloride-6.136g, Sodium Hydrogen Carbonate -2.940g, Calcium Chloride Dihydrate-0.2205g, Magnesium Chloride Hexahydrate-0.1017g, Glucose anhydrous-1.000g; Fresenius Medical Care Deutschland GmbH-Germany
NovoMix 50 Flexpen 100 U/ML; Insulin Asart Biphasic(rDNA)-300 U; Novo Nordisk A/S/Denmark
NovoMix 70 Flexpen 100 U/ML; Insulin Aspart Biphasic(rDNA)-300 U; Novo Nordisk A/S/Denmark
Olysio Capsules 150mg; Simeprevir-150mg; Janssen-Cilag Int. N.V./Belgium
Omeprazole Normon Powd. For Soln. for Infn. 40mg; Omeprazole-40mg; Lab. Normon S.A. /Spain
Ondansetron Normon Injectable Soln. 4mg/2ml; Ondasetron-4mg; Lab. Normon S.A. /Spain
Ondansetron Normon Injectable Soln. 8mg/4ml; Ondasetron-8mg; Lab. Normon S.A. /Spain
Ondansetron Normon Tablets 4, 8mg; Ondansetron-4, 8mg; Lab. Normon S.A. /Spain
Opsumit Tablets 10mg; Macitentan-10mg; Actelion Pharma Ltd./Switzerland
Paracetamol IV Infn. 1g/100ml (glass bottle); Paracetamol-1g; KSPICO-Kuwait
Piramyl Tablets 6mg; Glimepiride-6mg; Tabuk Pharm. Mfg. Co. /KSA
Propess Vaginal Delivery System 10mg; Dinoprostone-10mg; Ferring GmbH/Germany
Rapiclav Tablets 1g; Amoxicillin -875mg Clavulanic Acid-125mg; IPCA Lab. Ltd./India
Reducar Capsules 10, 20mg; Isotretinoin-10, 20mg; Gap S.A. - Greece
Replagal Conc. for Soln. for Infn. 1mg/ml; Agalsidase Alfa -1mg; Shire Human Genetic Therapies AB/ Sweden
Replagal Conc. for Soln. for Infn. 3.5mg/3.5ml; Agalsidase Alfa -3.5mg; Shire Human Genetic Therapies AB/Sweden
Sovaldi Tablets 400mg; Sefisvyvua-400mg; Gilead Sciences Intd. Ltd./U.K.
Stelara Soln. for Injn. 45mg/0.5 ml (PFS); Ustekinumab (rDNA)-45mg; Janssen-Cilag Int. N.V./Belgium
Stelara Soln. for Injn. 90mg/ml (PFS); Ustekinumab (rDNA)-90mg; Janssen-Cilag Int. N.V./Belgium
Tazret Forte Cream 0.1% w/w; Tazarotene-1mg; Glenmark Pharma Ltd.-India
Vimpat Solution for Infn 10mg/ml; Lacosamide-200mg; UCB Pharma S.A./Belgium
Vimpat Syrup 10mg/ml; Lacosamide-10mg; UCB Pharma S.A./Belgium
Vimpat Tablets 50, 100, 150, 200mg; Lacosamide-50, 100, 150, 200mg; UCB Pharma S.A./Belgium
Vitamin Syrup; Many ingredients; Medpharma Pharm. & Chem. Ind. (LLC) /U.A.E.
Wilfactin Pwd. & Solvent for Soln. for IV Infn.1000 IU/10ml; Human Von Willebrand factor 1000 IU Water for Inj. -10ml; LFB Biomedicaments/ France
Wilfactin Pwd. & Solvent for Soln. for IV Infn.2000 IU/20ml; Human Von Willebrand factor-2000 IU Water for Inj. -20ml; LFB Biomedicaments/ France
Wilfactin Pwd. & Solvent for Soln. for IV Infn.500 IU/5ml; Human Von Willebrand factor-500 IU Water for Inj. -5ml; LFB Biomedicaments/ France
Xtandi Capsules 40mg; Enzalutamide; Astellas Pharma Europe B.V. – The Netherlands
Zakon Tablets 200mg; Cefpodoxime-200mg; Medpharma - U.A.E.

Answers to: Test your knowledge

Correct answers:
1-A; 2-E; 3-C

The *Kuwait Pharmacy Bulletin* (ISSN 1028-0480) is published quarterly by the Faculty of Pharmacy, Kuwait University, and includes a list of recently approved drugs from the MOH. It aims to provide instructive reviews and topical news items on a range of drug related issues. It is widely distributed free within the university, to hospitals, polyclinics & private pharmacies as well as to other universities within the Gulf & Middle East region.

The information in this bulletin does not necessarily reflect the views of the editorship, nor should it be taken as an endorsement of any product that is mentioned herein. Articles are generally adapted from literature sources and rewritten or occasionally reproduced with permission from the appropriate sources.

Readers wishing their own copy may ask to be added to the mailing list by contacting the Executive Editor.

***Executive Editor*: Yunus Luqmani. *Assistant Editors*: Leyla Hasan Sharaf, Samuel Koshy**

Editorial Office: Faculty of Pharmacy, Health Sciences Centre, Kuwait University, PO Box 24923 Safat, 13110 Kuwait, Fax:25342087; email: yunus@hsc.edu.kw