



DRUG ALERT

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New Drugs

Retigabine - a novel drug with novel mechanism for epilepsy

Epilepsy characterized by excessive neuronal discharge is currently treated with antiepileptic drugs directed towards sodium, calcium and gamma amino butyric acid (GABA) channels. So far little focus has been paid towards voltage-gated potassium ion channels, though they have a major role in the control of neuronal excitability. Their role has been confirmed by studies showing relationship between functional impairment of potassium channels and epilepsy. This led to the discovery of retigabine a novel anticonvulsant, unrelated to any of the available antiepileptic drugs. Its action is primarily mediated by opening neuronal voltage-gated potassium channels KCNQ2/3 and KCNQ3/5. In addition to this unique action, retigabine also potentiates GABA-evoked currents in cortical neurons at high concentrations.¹

Clinical trials have reported the effective tolerable dose range for retigabine to be 600-1200 mg/day. Retigabine is rapidly absorbed orally, metabolized by liver and excreted through kidney. Gender differences were found as female subjects showed higher plasma concentrations following single oral administration of 200 mg retigabine compared to male subjects.

Adverse effects of retigabine includes mild dizziness, headache, asthenia, nausea and somnolence. At higher doses, retigabine was associated with chills, pain, myalgia, symptomatic hypotension, sweating and vomiting.^{2,3}

Abraxane - next generation paclitaxel

Abraxane (ABI - 007) approved by US FDA for the treatment of breast cancer is an albumin stabilised nanoparticle formulation of paclitaxel.¹ The anticancer drug paclitaxel is poorly soluble and is associated with infusion related hypersensitivity reactions. Its solubility in abraxane is enhanced by adding micelle forming vehicle cremophor EL. In a study, conducted on breast cancer patients, abraxane at a maximum tolerated dose of 300 mg/m²/week showed no infusion related hypersensitivity reactions.²

CONTENTS		
New Drugs	-	1
Centre's Report	-	2
Case Report	-	3
ADR Alert	-	3
Quiz	-	4

Conclusion

Retigabine has successfully completed Phase II clinical trial for the treatment of epilepsy. Currently it is undergoing phase III trials.⁴ Retigabine is unique as it selectively activates potassium ion channels in the neurons, thus avoiding cardiac side effects.³ *In vitro* models suggest that retigabine is likely to be useful in resistant epilepsy. Clinical data obtained so far indicate that retigabine is well tolerated in humans at therapeutic dose range. Hence, retigabine may prove to be of use in the treatment of epilepsy where neuronal hyperexcitability is an underlying factor.

References

1. Rogawski MA *et al.* *Curr Neurol Neurosci Rep* 2008;345-52.
2. Hermann R *et al.* *Clin Pharmacol Ther* 2003; 61-70.
3. Wuttke TV *et al.* *Mol Pharmacol* 2005; 1009-17.
4. Porter RJ. *Neurotherapeutics* 2007; 149-54.

Similarly another trial with abraxane, on breast cancer patients with metastasis showed an overall response rate of 33% compared to 19% with paclitaxel.³ These studies have shown that albumin bound paclitaxel is more safe and effective than paclitaxel alone. Recently a newer formulation of paclitaxel namely Genexol - PM, without cremophor EL is currently under trial for breast carcinoma. In phase 1 trial, with patients of refractory malignancies it was found to be superior to paclitaxel at a dose of 300 mg/m². However, at

this dose adverse effects like neuropathy, myalgia and neutropenia were seen.⁴

Precautions to be taken in*:

a) pregnancy as it has caused fetotoxicity in animal studies. b) Patients with neutrophil less than 1500 cells /mm³. c) Children as safety has not been established in paediatric group.

Exubera – the fall

Insulin with well established safety and tolerability has been playing a unique role in the management of diabetes mellitus. The major drawback with insulin treatment is the route of administration as it can be given only through injection. Patients associate injections with pain and inconvenience and this delays initiation of insulin treatment by the physicians. Availability of insulin through a noninvasive route can encourage patients to accept insulin therapy more rapidly and readily. Among the alternative routes, pulmonary route seems to be more promising. The first of inhaled insulin delivery system, exubera marketed by Pfizer, was approved by US Food and Drug Administration in January 2006.

Exubera is human rDNA insulin prepacked in 1mg and 3mg foil packets delivering 3 units and 9 units of insulin respectively. The dry powder is converted to aerosol by a handheld device. Inhaled insulin is rapid acting and attains a peak plasma concentration in 30-90 min with marked effect on fasting glycemia in humans.¹ Overall glycemic control as assessed by HbA_{1c} is similar to premeal subcutaneous regular insulin. Some of the adverse

References

1. Gardner ER *et al. Clin Cancer Res* 2008;14:4200-5.
2. Ibrahim NK *et al. Clin Cancer Res* 2002;8: 1038-44.
3. Gradishar WJ *et al. J Clin Oncol* 2005;23: 7794-803.
4. Kim TY *et al. Clin Cancer Res* 2004; 10:3708-16.

effects of inhaled insulin like reduced pulmonary function and anti insulin antibody production found during the trials were of less clinical significance. Asthma and smoking were found to affect absorption of inhaled insulin and these people were considered inappropriate for inhaled insulin treatment.² Recently trials have shown that patients with past history of smoking on inhalational insulin were more prone to develop lung cancer. US Food and Drug Administration (FDA) has warned regarding this complication. Since only few patients were using exubera, it failed to meet the financial expectation of the company and Pfizer ceased marketing the product in October 2007.³

References

1. Eggleston EM *et al. BMJ* 2006; 332:1043.
2. Bellary S *et al. Diabetes Vasc Dis Res* 2006; 179-85.
3. <http://www.fda.gov/medwatch> as on 10-06-08.

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Centre’s Report

Number of Adverse Drug Reactions (ADR) reported from peripheral centers during the period of Jan to May 2008

S.No	Peripheral centres	No. of ADR reported (Jan to May 2008)	Percentage (%)
01	Coimbatore	NIL	0
02	Manipal	41	8.2
03	Bangalore	14	2.8
04	Kochi	74	14.8
05	Annamalainagar	143	28.6
06	Kolar	69	13.8
07	Mysore	153	30.6
08	Ooty	06	1.2

Number of Adverse Drug Reactions (ADR) reported from JIPMER during the period of Jan to May 2008

S.No	JIPMER, Pondicherry	No of ADR reported (Jan-May2008)	Percentage (%)
01	Doctors	65	55.08
02	Nurses	4	3.38
03	Pharmacists	2	1.69
04	MBBS students	47	39.83

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Case Report

Sildenafil: Ventricular tachycardia in a middle aged woman with pulmonary hypertension

A 38 year old woman developed sustained ventricular tachycardia (VT) after sildenafil citrate administration for pulmonary hypertension.

The woman had undergone ASD closure in 1993. She was on sildenafil citrate 25 mg BD for the past five years. She had presented with palpitations and the ECG showed ventricular tachycardia. The woman was kept in the medical intensive care unit where she developed fatal ventricular arrhythmias. The hypothesis that this woman had sustained VT due to sildenafil cannot be dismissed.

Concerns about the effects of phosphodiesterase-5 inhibitors on the heart and their safety in patients with cardiovascular disease have been raised. The concerns include effects on blood pressure, heart rate and cardiac electrophysiology. According to FDA reports on focused monitoring of ADRs of sildenafil, of the 130 confirmed deaths

among men (mean age, 64 years) who received sildenafil citrate, 77 had cardiovascular events, including 41 with myocardial infarction and 27 with cardiac arrest. Cause of death was unknown in 48 and noncardiac in 5 men.¹ Sildenafil citrate blocks the rapid component of the delayed rectifier potassium current in guinea pig hearts and produces small but significant increases in the QTc interval in humans.²

References

1. <http://www.fda.gov/cder/consumerinfo/viagra/safety3.htm>. Accessed on May 14, 2008.
2. Ilson BE, et al. *Journal of Clinical Pharmacology & Therapeutics* 2004;75: 47-53.

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ADR Alert

Known drugs, Unknown ADRs

First Reported Adverse Drug Reactions (ADR) in Recent Weeks

S.No	Drug	ADR reported	Reference
1.	Cotrimoxazole	Cryoglobulinaemia	Leclercq P <i>et al. Eur J Intern Med</i> 2008; 19:303-4.
2.	Daclizumab	Kaposi's sarcoma	Di Benedetto F <i>et al. J Cancer Res Clin Oncol</i> 2008;134:653-8.
3.	Etanercept	Chorioretinitis	Arriola-Villalobos P <i>et al. Eye.</i> 2008; 22:599-600.
4.	Etoricoxib	Exanthematous pustulosis	Lammintausta K <i>et al. ActaDerm Venereol</i> 2008; 88:200-1.
5.	Exenatide	Depression in elderly	Kohen I <i>et al. Int J Geriatr Psychiatry</i> 2008; 23:443-4.
6.	Fludarabine	Psoriasis	Jordan J <i>et al. Eur J Dermatol</i> 2008;18:365-6.
7.	Metronidazole	Anaphylaxis	Asensio T <i>et al. J Investig Allergol Clin Immunol</i> 2008;18:138-9.
8.	Pemetrexed	Fatal tumor lysis syndrome	Lee KY. <i>J Thorac Oncol</i> 2008;3:S88.
9.	Sunitinib	Pyoderma gangrenosum	Freyhaus K <i>et al. Br J Dermatol Epub</i> 2008 May 16.
10.	Trastuzumab	Ectopic pregnancy	Berveiller P <i>et al. Reprod Toxicol</i> 2008; 25:286-8.

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Quiz

1. What are TACE inhibitors and for which disease are they being tested as a treatment option in phase 2 trials currently?
2. The antiepileptic that causes change in the taste of carbonated beverages is.....
3. The drug that was approved in the treatment of constipation in 2006 which acts on chloride channels on the gastrointestinal epithelial cells is.....
4. The drug used for Attention Deficit Hyperactivity Disorder which has been withdrawn from market on account of hepatotoxicity is.....
5. The vasculitic disorder which responds best to steroid therapy is.....
6. Name the bacteria that has been found to enhance the effect of antitumor liposomal drugs in animal models?
7. For which group of disorders is imatinib mesylate currently being tested in animal models with success?
8. Name the only orally active direct thrombin inhibitor available in the market that has been approved by the European commission in 2008 for the prevention of venous thromboembolic events?
9. Name a drug that has been specifically found to inhibit the formation of advanced glycosylation end products in diabetes?
10. Name the earliest indicator for pulmonary toxicity in a patient on bleomycin treatment for testicular cancer?

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Answers

1. TNF alpha converting enzyme inhibitors in rheumatoid arthritis. 2. Topiramate. 3. Lubiprostone. 4. Magnesium pemoline. 5. Giant cell arteritis. 6. Clostridium novyi - NT. 7. Autoimmune rheumatic diseases. 8. Dabigatran etexilate. 9. Aminoguanidine. 10. Decline in the pulmonary diffusion capacity for carbon monoxide(DL_{CO}).

Guidelines for reporting of Adverse Drug Reactions

Regional Pharmacovigilance Centre, JIPMER, Pondicherry invites reports of all suspected adverse reactions to drugs and other medicinal substances, including herbals, traditional and complementary medicines, blood products, medical devices and vaccines.

Report even if:

- * The drug is an established one and the adverse drug reaction is well known
- * You are not certain the product caused adverse event
- * You don't have all the details

Who can report?

Any health care professional (doctors including interns, residents, dentists, nurses and pharmacists)

Where to report: You can report online at www.jipmer.edu or send your reports to:

Dr. C. Adithan, Coordinator

Regional Pharmacovigilance Centre (South)
Department of Pharmacology, JIPMER, Pondicherry-605006.

Note: If you are at JIPMER you can also use the yellow forms provided in wards.

Drug Information Service

- Have queries on therapy of disease?
- Want to know the safety of a drug?
- Need to know about drug interactions?
- Searching for information about new drugs?

We are here to help you

Drug Information Centre
Department of Pharmacology, JIPMER, Puducherry-6
Mobile No: 9791858689; Phone: 2272380; Ext: 3301, 3302.