Hertfordshire Partnership NHS
University NHS Foundation Trust

MEDICINES MANAGEMENT BRIEFING NOTE No 3

Restriction to the use of orphenadrine

NOVEMBER 2013 (UPDATED MARCH 2016)

In September 2013 the Drugs and Therapeutics Committee (DTC) discussed the issues around increased risk of toxicity with orphenadrine compared to other anticholinergic drugs, particularly in overdose. Current available evidence suggests that orphenadrine has the highest mortality among anticholinergics in overdose and its potential for abuse is likely to be similar to other anticholinergics. As there are other drugs with much lower toxicity, and no clear advantages of orphenadrine, routine use of orphenadrine should be discouraged.

The DTC has therefore decided to restrict the use of orphenadrine to a third-line choice, in patients who are not at risk of overdose. Orphenadrine 50mg tablets have since then been discontinued (Dec 2015), however orphenadrine oral solution 50mg in 5ml sugar free remains available as a third line option.

Formulary choices for management of antipsychotic induced extra-pyramidal side-effects:		
First choice	procyclidine	5mg tablets, 2.5mg/5ml oral solution (sugar free)
Second choice	trihexyphenidyl (benzhexol)	2mg tablets, 5mg tablets, 5mg/5ml oral solution
Third choice	Orphenadrine (only in those who are not at risk of overdose)	50mg in 5ml oral solution (sugar free)

Background and Evidence

Mental health disorders tend to carry a substantial risk of self-poisoning and suicide. One strategy to reduce deaths from self-poisoning is to identify the drugs which are more toxic in overdose than other drugs used for the same indication.

N Buckley et. al. examined the fatal toxicity of antipsychotic drugs and anticholinergic drugs for the years 1983-1992. The number of deaths in England and Wales due to acute poisoning by a single drug alone with or without alcohol co-ingestion[1] is shown in the table below:

Table 2 Fatal toxicity indices for anticholinergic drugs

	Deaths	Prescriptions (thousands)	Deaths per million prescriptions	95% CI
Orphenadrine	166	2320	71.5	61.1–83.3
Procyclidine	26	4259	6.1	4.0–8.9
Benzhexol	3	2199	1.4	0.3–4.0
Biperiden	0	14	0	0–267.3
Methixene	0	131	0	0–28.1
Benztropine	0	288	0	0–12.8
Total	195	9211	21.2	18.3–24.4

Data on prescriptions are for England only and are from the Prescription Costs Analysis system. The data up to 1990 ar not consistent with the data from 1991 onwards. Values in the tables may not add up to the total because of rounding.

Fatal toxicity of drugs used in the treatment of psychotic illnesses, N Buckley and P McManus, BJP 1998, *172:461-464* http://bjp.rcpsych.org/content/172/6/461.extract

From a retrospective study of a series of Norwegian cases on fatalities caused by anticholinergic drugs (1998) it was concluded that orphenadrine is responsible for a disproportionately high number of overdose deaths[2]. Of a total of 69 cases, orphenadrine was present in 57 (83%), *biperiden* in 8 (12%), procyclidine in 3 (4%) and trihexyphenidyl (benzhexol) in 1 (1%) of the subjects.

The mechanism of toxicity of anticholinergics is unknown but is usually attributed to quinidine-like effects on the heart and effects on a variety of other receptors (muscarinic, histamine and alpha adrenergic). Orphenadrine has complex pharmacokinetic properties and a narrow therapeutic index. Following an overdose, it confers toxic effects of rapid onset to several organ systems. No specific and effective therapy for orphenadrine intoxication has been established. Orphenadrine has pronounced toxicity in overdose causing seizures and cardiac arrhythmias[i].

Abuse potential

There is no strong evidence conferring one anticholinergic agent being more prone to abuse than others except for trihexyphenidyl (benzhexol), which seems to be abused the most. Until 1982 there was little information on the abuse of procyclidine, but anecdotal evidence and informal discussions with mental health pharmacists, psychiatrists, mental health nurses suggest that procyclidine is widely abused compared to orphenadrine, however the evidence seems to contradict this[3,4,5] or is lacking for such claims. Current evidence base suggests that no anticholinergic drug appears to be free from the potential for abuse. The misuse potential of anticholinergic drugs is another reason for choosing an anticholinergic with a large margin of safety[2].

References:

[i] Fatal toxicity of drugs used in the treatment of psychotic illnesses, N Buckley and P McManus, BJP 1998, *172:461-464* *http://bjp.rcpsych.org/content/172/6/461.extract*

[2] Fatalities caused by anticholinergic antiparkinson drugs: a retrospective study of a series of Norwegian cases Pål Gjerden, Karen Sofie Engelstad, Grete Pettersen, Lars Slørdal Tidsskrift for Den norske lægeforening 1998; 118: 42-44 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2670380/pdf/bcp0067-0228.pdf

[3] The use of anticholinergic antiparkinson agents in Norway, Epidemiology, toxicology and clinical implications, Pål GjerdenThesis for the degree of Doctor Philosophiae, Trondheim, November 2010, Norwegian University of Science and Technology Faculty of Medicine, Department of Laboratory Medicine, Children's and Women's Health. http://ntnu.diva-portal.org/smash/record.jsf?pid=diva2:378468

[4] Anticholinergic drug abuse: a common problem? G P Pullen, N R Best, J Maguire, British Med J Vol 289 8 Sept 1984 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1442870/pdf/bmjcred00518-0044.pdf

[5] Anticholinergic Drug Abuse and Misuse, Prof. Patricia A. Marken, Steven C. Stoner, Mark T. Bunker CNS Drugs, March 1996, Volume 5, Issue 3, pp 190-199