CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA
CONSULT #10,988

Consultant Reviewer:	Gwen L. Zornberg, M.D., Sc.D. Medical Officer ODE I/DPP
Consultation Requestor:	Jean Mackie DRUP
Date of Request:	January 22, 2007
Date Received:	January 30, 2007
Date Reviewed:	February 28, 2007

I. Background

DITROPAN (oxybutynin chloride), a muscarinic receptor antagonist was approved for the treatment of overactive bladder in adults with uninhibited neurogenic or reflex neurogenic bladder on March, 1997 and June, 2000. The commercial sponsors include Novartis, as noted on the consultation request sent to the Division of Psychiatry Products (DPP) by the Division of Reproductive and Urologic Products (DRUP). Pediatric exclusivity for the oxybutynin active moiety was granted on February 8, 2002. In a Post Marketing safety evaluation dated April 29, 2003 conducted by Evelyn R. Farinas, R.Ph., M.G.A., it was reported that in the interval between February 8, 2002 and March 19, 2003, the FDA received five pediatric reports, where the majority were from the US and all had a serious outcome. At that time, the reviewer concluded that the causality for adverse events in the five pediatric cases could not be attributed solely to oxybutynin (Ditropan) therapy.

II. Request for Consultation by DRUP

The one question asked in the consultation request form was as follows: "DRUP requests your assistance with a secondary review (e.g., to evaluate any causal relationships) of the enclosed post-marketing adverse event reports concerning CNS excitation reactions in children treated with Ditropan (oxybutynin chloride) for overactive bladder." Accompanying

the consultation were 3 collections of over 100 Medwatch reports (dating from 1/25/79 to the present).

III. Review of the submitted *Medwatch* Reports

Oxybutynin hydrochloride is a lipid-soluble, tertiary amine that inhibits the muscarinic actions of acetylcholine on smooth muscle. Oxybutynin also has a direct papaverine-like antispasmodic effect. In addition, it possesses a local anesthetic/analgesic effect. Oxybutynin has no antinicotinic effects at skeletal neuromuscular junctions or autonomic ganglia. The main indications are in the treatment of urinary frequency, incontinence, and nocturnal enuresis, as well as in uninhibited vesical hyperactivity after bladder surgery and chronic cystitis. Anticholinergic drugs have been used since the 19th century, when belladonna alkaloids were administered for the relief of symptoms of Parkinson's disease. Their use had declined because they were poorly tolerated, particularly by elderly patients.[1]

The reports in children in which oxybutynin was documented to be the only medication (without other medical conditions) are most informative when attempting to disentangle drug effects and attribute causality to this particular drug. There were some examples of such *MedWatch* reports in children with serious outcomes to support the occurrence of central anticholinergic toxicity associated with oxybutynin exposure in vulnerable children, at least as a contributing factor. In one report a six year old girl was exposed to oxybutynin 5 mg po qd beginning November 11, 1999, and after one week, the oxybutynin dose was increased to 5 mg po bid (as the only medication reported) for treatment of urinary incontinence due to a motor vehicle accident. Two weeks after starting oxybutynin, her grandmother reported that the child was experiencing visual hallucinations (e.g., seeing insects and bugs, thinking that her hands were bleeding) associated with "excitability". The physician reporter stated that the adverse event had abated with discontinuation of drug on December 13, 1999; he found oxybutynin to be causal, as the hallucinosis began after oxybutynin exposure and abated following discontinuation of the oxybutynin. The patient's grandmother reported that after this episode, the child had become "paranoid" and when she subsequently experienced "itching" sensations, the child insisted that someone check

[1] Donnellan CA, et al. Oxybutynin and cognitive dysfunction. BMJ 1997;315:13631-1364.

her to examine for insects crawling on her. In another case, oxybutynin was prescribed for the treatment of nocturnal enuresis in 9 year old boy who had been chronically anxious prior to oxybutynin initiation. After beginning treatment with oxybutynin, at night the boy experienced visual hallucinations upon awakening of a little green man with a large knife who he thought was threatening to him. After Ditropan was withdrawn, the hallucinosis resolved and the boy's sleep improved. Similarly, a seven year old boy prescribed Ditropan for nocturnal enuresis was reported to have experienced visual hallucinations coupled with a panic reaction after a month of treatment. In this report of an oxybutynin challenge/dechallenge exposure, after Ditropan was discontinued, the patient recovered. In a fourth report, on March 25, 1979, a physician reported that after 2 months of oxybutynin use to treat enuresis in the absence of concomitant medications, an 8 year old boy was reported to have developed the sudden onset of hallucinations, tachycardia and dilated pupils. The laboratory evaluation revealed a negative toxicology screen for other drugs. Finally, a challenge/rechallenge report was sent to a sponsor on September 29, 1988, in which a 4 year old girl experienced visual hallucinations during exposure to oxybutynin 10 mg po qd. Following this oxybutynin challenge, the physician re-challenged the patient with oxybutynin the following evening which led to the recurrence of visual hallucinations. After the physician discontinued the oxybutynin, the child's hallucinations were reported to have resolved without further problems.

In the scientific literature, the effects of central anticholinergic toxicity in children have been described in case reports of children exposed to drugs with anticholinergic properties as their principle mechanism of action (in which the anticholinergic symptoms described in the publication were similar to those noted in these *MedWatch* reports of pediatric cases)[2] as well as in epidemiologic studies of medication use in children in which anticholinergic adverse events were remarkable.[3] Consequently, in this compilation of varied oxybutynin spontaneous reports, the occurrence of adverse events

[2] Garza MB et al. Central anticholinergic syndrome from orphenadrine in a 3 year old. Pediatr Emerg Care. 2000;16:97-98.
[3] Levy L et al. Use of psychotropic drugs in th0 to 5 years old children in Aquitaine (France): prevalence and associated factors. Pharmacoepidemiol Drug Saf. 2006; 15:504-509.

characteristic of central anticholinergic toxicity such as hallucinations and anxiety associated with oxybutynin use are not unexpected based on its mechanism of action. Moreover, the challenge/dechallenge and then rechallenge in one case oxybutynin data (in an otherwise generally healthy patient) in the submitted reports who were not known to be exposed to concomitant medications provides support for the causality of the association.

In this compilation of spontaneous adverse event reports of a serious nature, certain children who cannot be predicted before treatment appear to be particularly vulnerable to the anticholinergic effects of oxybutynin. It should be noted that "CNS excitation" is a vague term and can represent many symptoms related to impairment of the central nervous system including symptoms from seizures to anxiety. These types of symptoms had been described in these differing reports. It is recommended that in the future "CNS excitation reactions", which is a vague term, be more clearly defined and specified. Within this compilation of spontaneously reported events over the years sent for review, there were numerous anticholinergic effects from the occurrence of severe drowsiness to psychosis that varied in severity and frequency. There were also differences between the reported individuals in terms of concomitant medications and medical illnesses that can exacerbate and/or confound the evaluation of undesired oxybutynin drug effects. With respect to CNS excitation, in a number of reports, there were descriptions of children who became anxious or whose anxiety was amplified in response to the onset of visual hallucinations. In one report, a new onset of seizures occurred with oxybutynin use, however, it was administered with a second agent that could account also for triggering the seizures. Nonetheless, the occurrence of central anticholinergic toxicity in vulnerable patients such as children, is not unexpected as such symptoms are consistent with the lipid-soluble oxybutynin's central antimuscarinic mechanism of action.

In view of the limitations of the data provided for this consultation the relationship between oxybutynin and the anticholinergic toxicity cannot be considered scientifically characterized or definitive. To begin with, in these spontaneous reports of unsystematically collected information, confounding influences such as unreported drugs or medical conditions can be a major cause accounting

for the reported anticholinergic symptoms. Furthermore, it is not possible to estimate the frequency of the reported CNS adverse events in children associated with oxybutynin use based on these reports to help gauge the potential risk with use.

IV. Conclusions and Recommendations

The reports in children cited above regarding anticholinergic symptoms such as hallucinosis, insomnia, drowsiness, tachycardia, and anxiety noted in the reports with oxybutynin challenge, followed by resolution of the symptoms on dechallenge, and coupled with one case of a recurrence of hallucinosis with oxybutynin rechallenge by the physician, provide support for a not unexpected causal association between oxybutynin use and central anticholinergic adverse effects such as hallucinosis, anxiety, and insomnia, as well as drowsiness. Based on the above concerns, caution should be advised to medical professionals and parents regarding the potential for central anticholinergic adverse effects in children with oxybutynin use. To better understand the relation between oxybutynin use and the frequency and severity of central anticholinergic symptoms in children, a well designed study of the relationship would be more informative.

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Gwen L. Zornberg, MD, ScD
Medical Officer
February 28, 2007
HFD-130

cc: NDA #20-771
NDA #21-288
HFD-130
HFD-130/GZornberg
/GDubitsky
/MMathis
/TLaughren
/SKaul
/DBerman

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/s/

Gwen Zornberg
2/28/2007 02:31:09 PM
MEDICAL OFFICER

Mitchell Mathis
3/1/2007 06:23:18 PM
MEDICAL OFFICER

Thomas Laughren
3/2/2007 09:05:03 AM
MEDICAL OFFICER