



Issue 24  
October 2001

# Issues in Emerging Health Technologies

## Transdermally-delivered Oxybutynin (Oxytrol®) for Overactive Bladder

### Summary

- ✓ **The oxybutynin patch is a transdermal delivery system, which releases the drug oxybutynin through the skin for the management of overactive bladder.**
- ✓ **Limited evidence suggests that transdermal delivery of oxybutynin over a short period of time may have efficacy comparable to oral oxybutynin.**
- ✓ **Recent phase II and III clinical trials supported by the manufacturer suggest a potentially reduced incidence of dry mouth compared to oral oxybutynin. Itching, however, is present in 18% of patients, and the patients' withdrawal rate due to adverse events after 12 weeks is significant (10%).**
- ✓ **More studies are required to determine the long-term efficacy and safety of the oxybutynin patch for overactive bladder.**
- ✓ **A New Drug Application for transdermal oxybutynin (Oxytrol®) is currently under review at the U.S. Food and Drug Administration. As of October 2001, the oxybutynin patch has not been approved in Canada.**

### The Technology

Overactive bladder is a symptom complex, which includes urinary frequency and/or urinary urge with or without urge incontinence.<sup>1</sup> Oxybutynin inhibits the contraction of the bladder by blocking the action of acetylcholine at the muscarinic receptor sites.<sup>2</sup>

Oxybutynin appears to be an effective oral antimuscarinic drug for overactive bladder;<sup>3</sup> however, its use is limited by common and sometimes intolerable side effects including dry mouth, constipation, blurred vision, impaired voiding and confusion, especially in the elderly.<sup>4</sup> A recent study

reported that among 231 women treated with antimuscarinic agents for detrusor instability (85% of whom received oxybutynin), only 18% remained on therapy after six months. The most common reason for discontinuing treatment was adverse effects.<sup>5</sup> The side effects of the drug likely arise from its metabolite, N-desethyl oxybutynin which is present in the plasma at concentrations of four to ten times that of the parent compound.<sup>6,7</sup>

A transdermal delivery system was developed in an attempt to decrease the active metabolite levels, and side effects, by avoiding presystemic metabolism in hepatic and intestinal enzyme systems.<sup>8</sup> This transdermal patch delivery system is composed of a permeation enhancer contained in an adhesive matrix which holds the active drug oxybutynin.<sup>9</sup>

### Regulatory Status

The oxybutynin patch is manufactured by Watson Pharmaceuticals, Inc. who filed a New Drug Application to the United States (U.S.) Food and Drug Administration in April 2001. As of October 2001, the drug has not been approved in Canada.

### Patient Group

Overactive bladder is a common disorder. It can affect persons of any age, and the prevalence tends to increase with age. A recent survey of 16,000 adults 40 years of age or older shows 17% of respondents reported having overactive bladder symptoms with 14% reporting frequency, 9% urgency and 6% urge incontinence.<sup>10</sup> According to the National Advisory Council on Aging, 1997, an estimated one million Canadians are affected by urinary and faecal incontinence. In Canada, 20% of seniors experience the disorder. In Canadian households, 17.7% of females and 8% of males have urinary incontinence and among seniors living in institutions, 37% of men and women have daily urinary incontinence.<sup>11</sup>

## Current Practice

The management of overactive bladder involves non-pharmacological approaches and pharmacotherapy. Non-pharmacological approaches include the use of incontinence pads, bladder training, pelvic floor exercises, biofeedback, intermittent self-catheterization and electrical stimulation.<sup>12,13</sup> Implants generating electrical impulses to stimulate sacral nerves, which control the bladder and pelvic floor muscles, have been used successfully in patients with overactive bladder who have failed some of the more conventional treatments.<sup>14</sup> More invasive surgical procedures such as bladder neck suspension surgery and augmentation cystoplasty are rarely performed and are reserved for people who consistently fail to respond to conservative treatment measures.<sup>15</sup>

Pharmacotherapy is the main treatment option and includes anticholinergic medications, tricyclic drugs, alpha adrenergic agents and estrogen preparations.<sup>16,17</sup> Antimuscarinics such as oxybutynin, scopolamine, propantheline, and hyoscyamine are partially effective; although side effects such as mouth dryness, blurred vision and constipation can limit their use.<sup>18</sup> Better-tolerated medications are now available including slow-release oxybutynin, and the more bladder specific antimuscarinic agent, tolterodine. Slow-release oxybutynin has been shown to have comparable efficacy to immediate-release oxybutynin, with a lower incidence of side effects.<sup>19,20</sup> Clinical results show that the efficacy and safety of both immediate-release and slow-release tolterodine in an overactive bladder is equal to that of oxybutynin, but tolterodine is better tolerated by the patients.<sup>21,22</sup>

## Administration and Cost

The oxybutynin patch is applied on the abdomen, buttock or hip and changed twice a week. No cost information about the oxybutynin patch (Oxytrol®) is currently available.

## Rate of Technology Diffusion

Although overactive bladder is recognized as a common disorder, its prevalence may still be underestimated. Patients are often reluctant to discuss bladder symptoms with their physicians, and older patients may assume that the symptoms of

overactive bladder are the normal consequence of aging. Some patients may be embarrassed by the disorder or have a fear of invasive testing and adverse effects from currently available drugs. It is difficult at present to estimate the number of patients for whom the oxybutynin patch may be prescribed. However, given the large number of patients suffering from overactive bladder, a drug with better tolerability could be attractive.

## Concurrent Developments

Different drugs are under study for this disorder, with the goal of increasing the selectivity of the drug for the bladder, and decreasing the anticholinergic adverse effects. Darifenacin (an M3 receptor-selective antimuscarinic) and S-oxybutynin (a S-isomer of oxybutynin) are in early phase III clinical trials. The subtype-selectivity of darifenacin may improve the selectivity for the muscarinic M3 receptors involved in bladder contraction<sup>23</sup> and the S-enantiomer form of oxybutynin may retain spasmolytic activity while reducing its antimuscarinic-induced side effects.<sup>24</sup> Alternative routes of administration such as intravesical instillation and rectal administration may also reduce the drug metabolite levels. These have been used for oxybutynin, atropine, local anesthetics and capsaicin.<sup>25,26</sup>

## The Evidence

The short-term efficacy, safety and tolerability of transdermal versus oral oxybutynin in adults with urge urinary incontinence were studied in a 6-week, randomized phase II study with 76, mostly female patients.<sup>27</sup> Most patients began the study at the first dose level, which was 2.6 mg/day transdermally or 10 mg/day orally. Dose titration followed after the first two weeks to achieve the maximal tolerable dose. The study found that transdermal oxybutynin when compared to oral oxybutynin provided a comparable decrease in incontinence episodes per week (34 vs. 33,  $p = 0.39$ ), but less side effects incidence (38% vs. 94%,  $p < 0.001$ ) and a lower metabolite/oxybutynin ratio (1.2 " 0.5 ng/mL vs. 5.3 " 2.1 ng/mL). Erythema at the oxybutynin patch occurred in 38% of patients, with 8% being moderate to severe erythema. Only patients with known improvement on oxybutynin were studied in this trial, the effect size reported may therefore be exaggerated in favour of the oxybutynin patch.

In a randomized, placebo-controlled phase III study, 520 patients with overactive bladder received a placebo patch, or patch delivering 1.3 mg/day, 2.6 mg/day, or 3.9 mg/day of oxybutynin.<sup>28</sup> The patches were applied twice a week for 12 weeks, followed by a 12-week open label, dose titration phase. Most of the patients were female. The response to the two lower doses of oxybutynin was comparable to the placebo ( $p = ns$ ). The 3.9 mg/day dose showed a better efficacy ( $p < 0.05$ ) and a comparable incidence of systemic side effects than the placebo. Improvement in quality of life was reported in the treatment group, but no details were given regarding the methodology used. One reported adverse effect was itching which occurred in a significant number of patients with the oxybutynin patch.

### Phase III Clinical Trials

	Incontinence Episodes (decrease per week)	Frequency (decrease per day)	Urine Volume Increase (mL)	Dry Mouth (% of patients)	Constipation (% of patients)	Itching (% of patients)
Transdermal oxybutynin 3.9 mg/day	19	2.0	24.0	8.8%	<1%	18%
Placebo	14.5	1.0	6.0	8.3%	3%	

It is noteworthy that the withdrawal rate due to adverse effects was 10% (53 out of 520 patients), with approximately one-half (25 or 4.8%) due to application site reactions. Since the information is not broken down by groups, the withdrawal rate in the treatment group is not known. In previously published unrelated studies, the withdrawal rate due to tolterodine 2 mg bid, oxybutynin 5 mg tid, tolterodine slow-release 4 mg qd, and oxybutynin slow-release 10 mg qd were 8%, 20%, 5.3% and 0%, respectively.<sup>29-32</sup>

## Implementation Issues

Much more evidence is required before this new product can be determined to be a worthwhile addition to the pharmaceutical possibilities for the management of overactive bladder. For example:

- More studies are needed to examine the long-term efficacy of transdermal oxybutynin and its impact on quality of life.
- Studies carried out on male and pediatric patients are required.

- The advantages of transdermal oxybutynin must be measured against drugs with better selectivity for the bladder, or those with fewer antimuscarinic side effects, such as tolterodine and slow-release oxybutynin.
- Studies directly comparing transdermal oxybutynin and other delivery systems of oxybutynin such as intravesical instillation, rectal administration would be useful.

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This brief was prepared by Dr. Chuong Ho; CCOHTA and has been peer reviewed. The contents are current as of October 2001.

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ISSN 1488-6324 (online)  
ISSN 1488-6316 (printed)  
Publications Agreement Number 40026386