

hours after the overdose, showed no abnormalities. Concentrations of cetirizine in the blood and urine samples, collected 14 hours after the overdose, confirmed an intake of approximately 180 mg of cetirizine (2.4 µg/ml and 129.0 µg/ml, respectively). After a washout period of 3 days, the patient resumed taking his trial medication as prescribed and has exhibited no further clinical signs or symptoms relating to the overdose.

In this report the toddler tolerated the overdose with virtually no complications. Obviously, a single case is no proof for definite harmlessness of a major overdose. It should be noted that the commercially available form of cetirizine drops has a child-proof stopper, which would have prevented the incident described.

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1/8/79714

Topical triclosan treatment of atopic dermatitis

To the Editor:

Kolmer et al. (J Allergy Clin Immunol 1996;98:702-7) recently reported the efficacy of itraconazole in the treatment of severe intractable atopic dermatitis. Any nontoxic treatment advance is to be applauded. We have been impressed with the daily use of a topical antiseptic wash containing 1% wt/vol triclosan (Irgasan DP 300, a synthetic diphenyl ether, 5-chloro-2-[2,4-dichlorophenoxy] phenol) in the treatment of infants and children with moderate to severe eczema. It is available, here in Australia, combined with a moisturizer and emollient as Microshield T (Johnson & Johnson Medical Pty. Ltd.). Triclosan has been shown to be an effective antimicrobial, useful in the eradication of methicillin-resistant *Staphylococcus aureus*,¹ an effective antifungal agent,² and to have antiinflammatory actions. It has been reported to markedly reduce the wheal produced by intradermal histamine,³ to reduce the effects of topical applications of nickel in sensitized individuals, to reduce the effects of topical applications of sodium lauryl sulfate, and to inhibit the cyclooxygenase and lipoxygenase pathways of arachidonic acid production and prostaglandin E₂ production in vitro. It has a low toxicity and a very low incidence of contact sensitization, and it is tolerated on weeping eczema. It is even being studied as an oral rinse for the treatment of gingivitis.

Topical triclosan appears to be worth considering in the treatment of atopic dermatitis because bacterial infections have a significant role in provoking cutaneous inflammation. In addition, triclosan's antiinflammatory and antifungal action may provide additional benefits.

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1/8/80977

Flovent (fluticasone propionate inhalation aerosol)

To the Editor:

Flovent (fluticasone propionate [FP]) inhalation aerosol is currently marketed in the United States by Glaxo Wellcome. The pivotal clinical trials of FP that were presented to the Food and Drug Administration (FDA) were performed with a 10% wt/wt lecithin suspension; after the trials were undertaken, the concentration of lecithin was reformulated to 1% wt/wt to assure dose-to-dose consistency.¹ The original 10% formulation was 20% bioavailable,¹ whereas the reformulated 1% suspension, which is being marketed worldwide, is 30% bioavailable (Flovent package insert).

On my inquiry to Glaxo Wellcome's Medical Services Department, on August 8, 1996, a pharmacist/drug information scientist sent information regarding the reformulation of FP (Correspondence, Glaxo Wellcome Medical Services Department; August 26, 1996). The report stated, "The ratio of mean AUC₂₄ between the 1% formulation and the 10% formulation was 1.19 (90% CI: 1.05-1.35; p=0.024), the ratio of AUC_{last} was 1.25 (90% CI: 1.06-1.48; p=0.034) and the ratio of mean C_{max} was 1.30 (90% CI: 1.15-1.58; p=0.002). Since the 90% confidence intervals were outside the FDA accepted criteria of 0.80-1.25 for oral dose forms, a formal bioequivalence statement could not be made."

Further clarification of the reformulation was requested, and on August 26, 1996, a revised information sheet was sent, and one of the revisions was the deletion of the statement, "Since the 90% confidence intervals were outside the FDA accepted criteria of 0.80-1.25 for oral dose forms, a formal bioequivalence statement could not be made." (Correspondence, Glaxo Wellcome Medical Services Department; August 26, 1996)

In the Proceedings of the Pulmonary-Allergy Drugs Advisory Committee meeting of September 25, 1995, at which time FP was under review, on page 151 an FDA reviewer states, "In terms of safety, we also have some concern that the pharmacokinetic endpoints showed that the 1% was more bioavailable. So if we believe that, it means that systemic side effects may be a more serious concern with the 1% than the 10%. So on safety, we think the clinical studies and the PK studies do not conclusively show that the two are equivalent."¹

We as physicians must be given access to this type of information so that we can make informed choices for our patients. The pharmaceutical industry has the responsibility to provide a balanced database of information regarding their products.

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1/8/80979

Reply

To the Editor:

The letter from Dr. Levy contains some inaccuracies and misconceptions based, no doubt, on nationwide mailings to physicians from competitor drug companies. The formal comparison of the 1% and 10% lecithin MDI formulations was carried out in a study in which 24 healthy subjects received 880 µg of fluticasone propionate (FP) from both products in a crossover design. Blood samples were collected for 24 hours. This study showed that the median FP plasma concentration-time profiles were virtually superimposable and that the systemic effect, as judged by urinary cortisol excretion, was almost identical. As Dr. Levy was informed, the ratio of the geometric means for area under the curve over 24 hours was 1.19 (1%:10%) with 90% CI, 1.05-1.35. According to bioequivalence criteria for oral dose forms, for which 90% CI are required to be 0.80-1.25, the MDIs could not be judged bioequivalent. However, the Food and Drug Administration (FDA) has subsequently revised these intervals for highly variable drugs (90% CI 0.70-1.43)¹ and for generic albuterol MDI formulations (90% CI 0.67-1.50)² in which bronchoprovocation or bronchodilation is being measured, recognizing that inhalation technique plays a large part in determining lung deposition. With these newer quoted values, the FP MDIs would be judged bioequivalent.

A major misconception is that the marketed formulation of Flovent (1% lecithin) is significantly more bioavailable than the earlier 10% lecithin formulation. The early estimate of approximately 20% (for the 10% formulation) was based solely on areas under the FP curve over 8 hours in 96 healthy volunteers who took part in a number of different studies. The definitive absolute bioavailability study (with the 1% formulation), in which 12 healthy subjects received both intravenous and inhaled FP in a crossover design study, with blood samples taken

over 24 hours, gave rise to an average bioavailability of 30% exactuator but with considerable variability. It is inaccurate to say that the 1% formulation is significantly more bioavailable than the 10% formulation on the basis of the early estimate. It should be noted that an estimate of drug absorption through the lungs in healthy volunteers may overestimate absorption in patients with asthma.

According to the Medical Officers Review,³ "From the discussions (internal and at the advisory committee meeting) it was concluded that the data linking the 1% and 10% lecithin formulations taken together with other data in the NDA were reasonable enough to be used to support the approval of the 1% lecithin MDI. It was felt that the size of the difference in the bioavailability between the two formulations seen in the [pharmacokinetic] study may not be of clinical significance especially since no significant difference was seen in the HPA axis measurements in that study."³ After the advisory committee meeting and before approval of Flovent, the FDA had full access to all data pertaining to Flovent including data for 1200 patients treated in six additional studies demonstrating an indistinguishable efficacy and safety profile from that obtained with the 10% formulation.

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2. FDA Generic albuterol MDI interim bioequivalence interval is 67% to 150%. The Pink Sheet February 19, 1996:12.
3. Medical Officer's Review of NDA 20-548. FDA February 27, 1996:106.

1/8/80980