

The FDA pharmacologist, Dr. L. L. Phillips, has reviewed the above report concluding that " * * * Lomotil is more toxic to the young animal than to the adult and that the liquid form is more toxic than the powder—perhaps due to increased absorption from the gastro-intestinal tract." Her recommendation was that " * * * weight proportional doses should be prescribed for children and that lower doses of the liquid than the powder should be recommended."

The reviewer cannot but wonder whether the acute studies in weanling rats can be extrapolated to human infants and children. The majority of deaths with Lomotil were accidental. There have been a paucity of deaths on therapeutic—dosages after 6 years of use of the drug. The drug was approved 9/15/60 and 1/17/61. The study on dosages in a large number of children, supposedly near completion, is awaited before a request for dosage studies and absorption studies may be requested.

Conclusions

The drug is safe as originally approved. Efficacy is being evaluated by the appropriate NAS-NRC panel.

Recommendations

1. The supplement and reports reviewed be permitted under 130.9(d) of the regulations.
2. The company be requested to revise the package insert as recommended.

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PHARMACOLOGIST'S SUMMARY

Name of Drug.—Trade: Lomotil.

Generic: Diphenoxylate hydrochloride with atropine sulfate.

Dates of Supplement.—Supplement August 9, 1965 and September 16, 1965. Annual Report August 30, 1966.

Therapeutic Indication.—Antiperistaltic agent.

Usual Human Dose and Route.—To 20 mg/day for adults in divided doses, orally.

Material Reviewed.—Two reproduction studies from Huntingdon Research Center, Huntingdon, England. One acute toxicity study from Searle Toxicity Lab. July 20, 1965.

Summary

Teratologic studies have been performed on three animal species: rabbit, rat, and mouse at doses of 0.4, 4.0 and 20.0 mg/kg/day of Lomotil equal to 1X, 10X and 50X human therapeutic dose (HTD). There was no evidence of anomalies in any of the fetuses. This included 69 rabbit, 91 rat, and 105 mouse fetuses at the two higher doses. Abnormalities in all species were found on thalidomide (150–200 mg/kg) used as a positive control in the ratio of 6/6 rabbits, 1/56 rats, and 4/32 mice. Resorptions and stillbirths were similar in the test and negative control groups but higher in the positive control in rabbits and rats. There was a slight reduction with borderline significance in fetal weight in the mice given Lomotil but the differences were not dependent.

In a different series on long term subacute toxicity studies carried out on male and female rats with feeding 10X and 50X HTD for 80 days prior to mating and then throughout three cycles of pregnancy and weaning there were no differences in mortality of the adult groups. Food consumption for the first 8 weeks did not vary significantly but was slightly elevated in males and slightly decreased in females of all test groups. Weight changes reflected the food consumption for this period with an increase for males and a decrease for females.

Fertility in terms of percent pregnancies and size of litters was depressed in animals receiving 20 mg/kg/day Lomotil, and thalidomide. Neonatal loss was also greater in these two groups but losses were high in all groups due to handling. The decreased fertility on the high dose of Lomotil and on thalidomide was accentuated in the 2nd and 3rd matings. No anomalies were observed in 143 young at 4 mg/kg level or 45 young at 20 mg/kg level. Two abnormalities appeared in the first pregnancy on thalidomide and 4 in the second from a total of 33 offspring.