

As a eupheriant or a euphorogenic agent 60 mgs. of R1132 is more effective than 30 mgs. of morphine or 90 mgs. of codeine. It is roughly $\frac{1}{2}$ as potent as morphine and 1 and one half times as potent as codeine in this respect. The peak effect with codeine was in one to two hours and with R1132 was in four to six hours, however, the effect lasted much longer with R1132.

R1132 proved to be an effective suppressor of abstinence from morphine. It was more effective than codeine in this respect. Long-term studies in persons who were not addicted and who received the drug for an average of 57 days produced sleepiness, depressed respiratory rate, and produced abstinence effects.

A short double-blind direct addiction test of 18 days duration showed that patients developed constriction of the pupils, considerable sedation, constipation, and pruritus plus nausea. Compared to morphine and codeine it had more sedative effect than epiete effects. The intensity of the abstinence syndrome was only slightly less severe than from codeine withdrawal but significantly less severe than from morphine withdrawal.

The continuous administration of R1132 was associated with a low incidence or morphine-like subjective effects but with definite morphine-like changes in behavior and was associated with a moderate degree of physical dependence.

The incidence of nonnarcotic symptoms was far greater from R1132 than from codeine. It was concluded that when R1132 was administered on a temporary "Euphoregenic" schedule the patients liking for the drug was comparable to that of codeine. Since the doses of morphine, codeine, and R1132 used in these euphorogenic studies were from 3 to 16 times those which would be used clinically for controlling diarrhea it was apparent that addiction to any of these drugs is not likely to occur if given orally under strict medical supervision for the purpose.

Comment

This careful study clearly outlines that this drug is a narcotic with addicting potential and ability. There is no doubt that it can stop diarrhea and produce constipation, but it also can produce opiate-like effects. With this in mind I will review the presently approved labeling for the drug as well as recent advertising promotional material in medical journals.

The final printed labeling for this drug was submitted on September 15, 1960 and was acknowledged as effective by Dr. Madigan in a letter dated September 29, 1960. I will now review this labeling to see how well it correlates with the data in the two volumes of the NDA just reviewed.

The physicians brochure number 81 and the package insert seem to be identical and therefore the comment made about the statements in the brochure would apply to the package insert also. Immediately it becomes apparent again that the drug Lemotil, as promoted, is a combination of diphenoxylate hydrochloride with atropine sulfate where as all of the investigational studies both on man and animals and all of the clinical work was done on only diphenoxylate hydrochloride. In the investigational stage this was in the form of 5 mg. tablets, whereas for final use it's in the form of 2.5 mg. tablets. Also, it is well to point out that when given to the children in many cases it was given in a liquid form which was not part of the NDA. It is stated in the brochure that the subtherapeutic amount of atropine sulfate included in Lemotil is to discourage deliberate overdose. Each 2.5 mg. tablet contains .025 mgs. or $\frac{1}{2400}$ of a grain of atropine sulfate. Since the labeling permits up to eight tablets a day this would be a total of $\frac{1}{300}$ of a grain of atropine sulfate in 24 hours which is certainly within the therapeutic range. Atropine is not noted for being a good emetic and therefore it is difficult for me to understand how this would produce or would discourage deliberate overdose. In fact, deliberate overdose might produce atropine toxicity in addition to narcotic toxicity.

On page 3 of the brochure is the following paragraph, "Diarrhea has also been treated classically by the Administration of Narcotics such as camphorated tincture of opium, but such agents are frequently ever constipating, and they have a recognized addicting potential.

Comment

This paragraph is obviously misleading because it implies that this is not a narcotic and it implies that it is markedly different from camphorated tincture of opium which is paragoric. It also implies that this drug, Lomotil it not recognized as having an addicting potential, when, in fact the opposite is true. As a matter of fact this is the excuse given for adding atropine to Lomotil. Starting on page