

A METHOD FOR TESTING INTESTINAL IRRITANCY OF SUSTAINED RELEASE POTASSIUM CHLORIDE PREPARATIONS IN ANIMALS

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The assessment of the intestinal irritancy of sustained release potassium chloride tablets in small animals is rendered difficult by the size of the tablets, often too large for oral ingestion.

A surgical method has been devised using the anaesthetised rabbit whereby the duodenum is exposed by laparotomy: a small incision is made in the duodenum, the tablet introduced into the lumen and the incision sutured. The duodenal loop is replaced into the abdomen and abdominal incision covered by swabs. After four hours the rabbit, which has been kept anaesthetised, is killed and the intestine removed for inspection, photography and histopathology. This method is sufficiently quick and inexpensive to provide a rapid screening test.

The test was used to compare the relative local irritation and potential ulcerogenic effects of several commercially available slow release potassium chloride tablets and a new sustained release pellet form (Boehringer Ingelheim Ltd.) which was designed so that drug release was through a diffusion rate controlling membrane constituting the pellet coat and thus could not produce local high concentrations of potassium at mucous membranes. Most products produced moderate to severe irritation as indicated by bleeding and sometimes extensive tissue damage as indicated by necrosis; the sustained release pellets as such or in hard gelatin capsules produced no irritation. Even a batch of pellets chosen to give a much more rapid drug release than chosen for the specification for the batches for human use, gave no sign of damage when used in the above test. The capsules disintegrated in the test.

The effect of the sustained release pellets in capsules was also compared with those of slow release products of potassium chloride in rhesus monkeys, 15 of each sex, aged between 2 and 3 years and weighing 2 to 3 kg, i.e. large enough to accept the oral administration of the various products; the animals were killed after the morning dose on the fifth day of treatment by means of an i.v. overdose of pentobarbitone sodium and immediately exsanguinated by severance of the subclavian blood vessels. A detailed examination of the entire g.i. tract was made for macroscopic evidence of irritation, bleeding and ulceration. Also representative portions of the g.i. tract were removed, sectioned and examined histopathologically. Although the local damage by the release of potassium from the commercial product was in general less than in rabbits in which the products were more restricted in movement, the findings supported the general conclusions of the relative potential for damage of the various products shown in the experiments in rabbits.

The experiments in rabbits probably indicate what may happen at mucous membranes in man if a slow release product, for some reason, does not move steadily down the g.i. tract. The sustained release pellets, because of their distribution in the g.i. tract and their slow release of the drug did not give high concentrations of potassium at mucous membranes that produce tissue damage.