

## Diminished Effectiveness of a Second Administration of Atropine or Novatropin. Mechanism of Recovery.

J. P. QUIGLEY.

*From the Department of Physiology, Western Reserve University Medical School, Cleveland, Ohio.*

Administration of atropine preparations over a period of time leads in certain animals to a decrease in the effectiveness of the drug. Cloetta<sup>1</sup> found that normal rabbits excrete a dose of atropine during a period of 2 or 3 days but excretion is complete in one day according to Fickewirth and Heffter<sup>2</sup> if atropine is administered to rabbits habituated to the drug. Normal cats excrete very little atropine (Doebelin and Fleischmann<sup>3</sup>) but after habituation, the excretion is markedly augmented.

Another type of increased resistance to atropine preparations was noted in a series of experiments in this laboratory performed on fasting dogs and man in which objective records of gastro-intestinal motility were made by the balloon method. (The triple, tandem balloon was used in the human experiments.) It was thus determined that injection of an atropine preparation shortly after recovery (*i. e.*, return to preinjection tone and motility) from a preceding administration of atropine was less effective than the initial injection.

When administered as the initial medication, 0.065 mg./Kg. atropine intravenously administered to the unanesthetized dog uniformly completely inhibited the stomach and recovery was complete in  $80 \pm 30$  minutes. (Results of initial medications are presented in detail elsewhere.) Following complete return of preinjection tone and motility, a second injection of the same quantity of atropine (8 experiments) produced inhibition with recovery in approximately 30 minutes (3 experiments) or failed to produce complete inhibition (5 experiments). Reduced effectiveness from a second administration was likewise demonstrated when both the first and second dose were smaller (0.032 mg./Kg.) or larger (0.13 mg./Kg.). For example, the initial administration of 0.13 mg./Kg. produced complete gastric inhibition with recovery in  $150 \pm 30$  minutes. Repetition of this dosage after recovery (4 experiments) produced transient complete inhibition (3 experiments) or incomplete inhibition (1 experiment).

---

<sup>1</sup> Cloetta, *Arch. exp. Path. Pharm.*, 1911, **64**, 427.

<sup>2</sup> Fickewirth and Heffter, *Biochem. Z.*, 1912, **40**, 36.

<sup>3</sup> Doebelin and Fleischmann, *Z. klin. Med.*, 1913, **77**, 145.

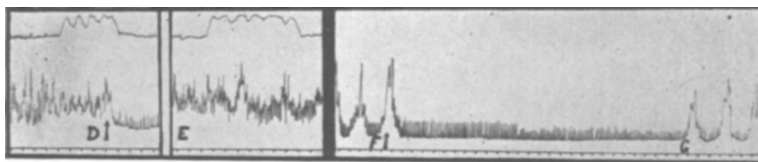


FIG. 1.

Effect of Novatropin and atropine on gastric motility.

Upper line, colon; mid-line, stomach; lower line, time intervals in minutes.

D. effect of intravenous injection of 0.065 mg./Kg., atropine sulphate, initial medication; E. early stage of complete recovery of stomach 62 minutes after injection.

F. following apparently complete recovery from a previous injection of atropine, injected intravenously 0.065 mg./Kg. atropine sulphate; G. early stage of complete recovery 29 minutes after injection.

Gastric hypermotility is produced by administration of insulin (Quigley, Johnson, Solomon<sup>4</sup>). This hypermotility in the normal human was uniformly completely inhibited by 0.65 mg. atropine administered subcutaneously when given as the initial medication and recovery was complete in  $45 \pm 15$  minutes. However, when given as the second injection (8 experiments), this dose either produced only a transient complete inhibition (5 experiments) or inhibition was incomplete (3 experiments).

Reduced effectiveness from repetition of administration was also observed with Novatropin (methylhomatropine bromide), a drug with an atropinelike action. Initially, 0.1 mg./Kg. in the dog always produced complete gastric inhibition with complete recovery in  $55 \pm 10$  minutes. After recovery, a second injection of this drug in 6 experiments produced no effect in one experiment, incomplete inhibition with complete recovery in 25 minutes in 3 experiments and in 2 experiments complete inhibition developed but was followed by full recovery in 45 minutes. As the initial medication, 0.2 mg./Kg. Novatropin in the dog produced complete gastric inhibition with full recovery in  $90 \pm 25$  minutes (3 experiments). A repetition of this dose failed to produce complete inhibition in 2 experiments and in one experiment inhibition was complete but full recovery occurred in 25 minutes. Similar results with Novatropin were obtained in man.

A decrease in effectiveness was obtained in the dog or human when atropine followed Novatropin or *vice versa*. This is illustrated by 3 experiments on man, in each of which 1.3 mg. atropine was given after recovery from 1.5 mg. Novatropin. In one experiment, complete inhibition developed but recovery was complete in 39 minutes. In another case, the region of the upper 2 balloons was

<sup>4</sup> Quigley, Johnson, Solomon, *Am. J. Physiol.*, 1929, **90**, 89.

completely inhibited for 31 minutes but the region of the lower balloon was unaltered. In the third experiment, the only effect consisted in a partial inhibition lasting for 3 minutes.

In 8 experiments with atropine and 6 experiments with Novatropin the second injection was found to inhibit motility of the colon in dogs as effectively as the initial injection of these drugs.

Although tolerance against the action of atropine preparations following chronic administration of atropine preparations is due to the development of an increased rate of elimination, this mechanism rather definitely does not explain the reduced effectiveness of a second injection as noted in our experiments. The return of preinjection gastric tone and motility is not an indication of complete disappearance of atropine or Novatropin from the organism but apparently occurs when the concentration is only moderately reduced. A further elevation of atropine or Novatropin concentration (probably to a level above the previous maximum) by administration of a second dose of these drugs may produce a partial inhibition of the stomach but the depression is usually only moderate because the tissue has developed a resistance to the action of these drugs; *i. e.*, the motility obtaining at the time of recovery exists in spite of the presence of the drug. This observation would have the important clinical indication that little effect on gastric motility or tone should be anticipated from a second administration of atropine preparations after recovery from a previous administration of this drug.

The colon probably also recovers motility in spite of the continued presence of atropine or Novatropin but at the time of recovery from the initial injection is less resistant to a further augmentation of the drug than is the stomach.