NERVE BLOCK BY MEPHENESIN *†

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MEphENESIN was introduced as a depressant of the central nervous system by Berger and Bradley (1). Upon analyzing its pharmacologic actions, these authors found that in higher concentrations mephenesin blocked nerve conduction, with a potency comparable to that of procaine. The relative nontoxicity of mephenesin given systemically and the unique features of the substance as a neural depressant made it seem desirable to investigate further its nerve-blocking action. Studies with isolated bullfrog's sciatic nerve showed that, in contrast to procaine hydrochloride, mephenesin readily penetrates the sheath and other barriers of intact nerve and blocks α and C fibers at approximately similar rates (2).

In this paper we report experiments exploring the possibility of using mephunesin as a nerve-blocking agent in human beings, along with histologic studies to detect possible damage under these conditions.

Mepheneresin Nerve Block in Guinea Pigs.—Mephenesin,*† 1 ml. of 1.3 per cent or 2 per cent solution, produced paralysis and loss of sensibility to painful stimuli when injected around the sciatic nerves in 4 guinea pigs. The block appeared to wear off more rapidly with 1.3 per cent mephenesin (fifteen and twenty-five minutes) than with 2 per cent procaine hydrochloride (forty and fifty-seven minutes). This is in accordance with the results of Davis et al. (3), who found that 10 per cent mephenein applied topically to the cornea produces local anesthesia lasting about one-eighth the duration of that produced by 10 per cent procaine. With 1 ml. of 2 per cent mephenein the block lasted about fifty to 100 minutes, and with 2 ml. of 1.3 per cent mephenein anesthesia lasted around 100 minutes. It is noteworthy

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† 1.3 per cent mephenein has approximately the same molarity as 2.0 per cent procaine hydrochloride, namely 0.072 M. The mephenein ("tolerol"," kindly supplied by Squibb & Co.) and the procaine hydrochloride solutions contain sufficient sodium chloride to make them isotonic and were diluted with 0.9 per cent sodium chloride as required.
that 1 ml. of 2 per cent procaine hydrochloride produced generalized convulsions in all our guinea pigs, but 1 ml. of 1.3 per cent or 2 per cent mephenesin produced no obvious generalized effects.

Mephenesin in a lower concentration, that is 0.65 per cent, failed to produce paralysis and loss of sensitivity to painful stimuli, whereas 1 per cent procaine hydrochloride did cause paralysis and anesthesia. This may indicate that the minimal effective concentration of mephenesin is greater for blocking mammalian nerves than that found for blocking frog nerve (2). Mephenesin may diffuse away from the site of injection more rapidly than procaine, and a higher concentration may be required in order to build up to the necessary blocking concentration of mephenesin within the nerve trunk.

II. Histologic Findings in Nerves Blocked by Mephenesin.—Clinically, mephenesin, 1 ml. of 1.3 or 2 per cent solution, when injected around the sciatic nerves produced no gross changes beyond the temporary nerve block in 3 of the guinea pigs. In a fourth animal anesthesia was still present at the time of sacrifice.

The animals were killed seventeen days after injection and the infiltrated tissue examined histologically. The nerves were stained by the Bielschowsky, Marchi and Kulschitzky methods and muscles with hematoxylineosin and van Giesen methods. No evidence of inflammatory or degenerative changes was found in muscle or nerve. There was no evidence of degeneration even in the nerve of the one animal which still showed functional block (paralysis and anesthesia) at the time of sacrifice; this leg had been injected with 2 per cent mephenesin. One other guinea pig, with 2 per cent mephenesin injected around both sciatic nerves, was sacrificed after three days in order to detect any acute effects. In this case, also, no histologic abnormalities were seen in the muscles or nerve.

Intrathecal Administration.—This procedure was carried out in one monkey by injecting 2 ml. of 2 per cent mephenesin into the subarachnoid space at the level of the cauda equina. The animal was being held in a sitting position. There was almost immediate paralysis of the lower limbs. The paralysis soon began to involve the upper limbs, as if the mephenesin solution were rising in the spinal canal. On this assumption, the animal was laid down in the horizontal position in order to reduce the possibility of the drug rising to the brain stem. Motor power began to return after ten minutes in the upper limbs, after about fifteen minutes in the lower limbs. The procedure was repeated fourteen days later with similar results, but motor recovery began after five minutes. Recovery from clinical effects was complete in both instances. The animal was killed about three weeks after the last procedure. Gross examination of the spinal cord and meninges revealed no abnormalities. Sections of the spinal cord and cauda equina were stained by Marchi and Nissl methods. No evidence of degeneration was found in the nerves, tracts or cell bodies.
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On the other hand, Davis et al. (3) reported that subarachnoid injection of 2 per cent mephenesin in rabbits may produce permanent paralysis in some of these animals.

Mephenesin as a Local Anesthetic in Man.—A cutaneous nerve well suited for such a study is a small twig of the superficial cutaneous branch of the radial nerve. It is easily accessible and accidental damage would be of little consequence. The nerve is easily located by having the subject extend the thumb so that the tendon of the extensor pollicis longus becomes prominent. The nerve can then be palpated where it crosses the tendon. Mephenesin, 0.5 to 1.0 ml. of 1.3 per cent solution, was injected around this nerve in several subjects and around the common peroneal nerve in one subject. The area of skin supplied by the nerve remained anesthetic for about fifteen to thirty minutes. A small area of anesthesia persisted in the region of skin where the mephenesin had been infiltrated. In 2 cases (one radial nerve branch and one peroneal nerve) anesthesia persisted for over a month in a part of the skin receiving the cutaneous nerve distribution away from the site of injection. All subjects reported an unpleasant burning sensation, persisting for some hours, at the site of the injection. In some instances, there was local erythema.

Mephenesin in a lower concentration, that is, 0.65 per cent, failed to produce paralysis or anesthesia when thoroughly infiltrated around the common peroneal nerve in one person, as was the case in the guinea pigs.

Discussion

The clinical potentialities of mephenesin as a local anesthetic agent are subject to further study since the present experiments were merely exploratory. The unpleasant local reaction and the semipermanent retention of hypesthesia probably make the drug unsuitable for routine purposes. The nature of the enduring functional block is unexplained and deserves further study, since no histologic changes could be detected in the one guinea pig that showed a local reaction. On the other hand, the persistence of hypesthesia may in fact be advantageous for certain clinical purposes, such as for the relief of some types of deep or chronic pain, including phantom pain associated with neuromas or trigger areas (clinical trials for such purposes have been instituted by one of us [B. F.]). The presumably high degree of penetrability of mephenesin across nerve sheaths (2) might make it useful for certain neuromas, scarred or sclerosed tissues, and so forth, that is in areas where individual nerves are diffusely located and difficult to inject.

Summary

The possible use of mephenesin as a nerve-blocking agent in human beings has been explored. Mephenesin, in concentrations of 1.3 per

§ We are indebted to Dr. J. B. de C. M. Saunders for this suggestion.
cent or more, is effective in blocking peripheral nerves and on intra
crhecal application (monkey). No histologic damage could be detected
in nerves and their surrounding tissues. Semipermanent anesthesia
was present in some instances and an unpleasant local reaction in all
cases. These factors seem to limit the usefulness of the drug. On
the other hand, the high diffusibility of mephenesin through nerve
sheaths (2) and its semipermanent nerve blocking effects may make
it especially desirable for some clinical conditions.

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