EFFECTIVE TREATMENT OF HICCUP WITH INTRAVENOUS METHYLPHENIDATE*

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HICCUP (singultus) is an intermittent clonic spasm of the diaphragm of reflex origin. With each contraction the bronchial lumen is constricted and in unintubated patients the glottis is closed. In mild cases unassociated with anaesthesia the spasm is usually a unilateral contraction of the diaphragm which spreads gradually across the whole muscle if the condition persists. The left side is more often affected than the right.¹ It is produced when a part of the reflex arc is stimulated. Afferents can arise from almost any part of the body, including the central nervous system, the vagus nerve, the phrenic nerve, or the sympathetic chain from T6 to T12. The centre of the reflex arc is located at cervical cord levels 3 to 5. The efferent limb is the phrenic nerve.²

Although no finite centre for hiccups has been located, it is believed that the respiratory and phrenic centres and the hypothalamic sympathetic centres work together as a specific hiccup centre.¹

Hiccupping in the awake patient is a nuisance and if prolonged may be exhausting. Under anaesthesia, it usually interferes with the surgeon's procedure. When hiccup occurs, the surgeon quite often complains that the patient is "bucking," implying that the patient is in a light plane of anaesthesia, which prompts the anaesthesiologist either to deepen the anaesthesia or to administer a muscle relaxant. The distinction between "bucking" and hiccupping, however, should be noted. "Bucking" is coughing or straining of the intubated patient in which there is forced expiration, the abdominal muscles are contracted and the diaphragm is in a position of ascent. Hiccupping is associated with an ineffective inspiration, the abdominal muscles are relaxed and the diaphragm is briefly in a position of descent.

CAUSES

Peripheral causes are irritations of the stomach, intestine, peritoneum, pleura, mediastinum, pericardium, or the diaphragm itself. The most common central causes are uraemia and diseases of the central nervous system. In some cases, the cause is thought to be psychogenic.^{1,3}

Hiccup during surgery is not a common complication of deep anaesthesia, but is the result of modern methods of "light" anaesthesia in which relaxation is produced by motor paralysis, and sensory reflex activity is, by comparison, relatively undepressed. It can be regarded as a reflex response to vagal stimulation.

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of the partially anaesthetized respiratory centres and incompletely paralysed peripheral musculature⁴

Areas in the central nervous system, particularly the medulla, also have been implicated in hiccups⁵

TREATMENT

Whenever there are numerous treatments for a disorder, none of them work well. This has been true in the treatment of hiccup. Previous treatment in the awake patient has included the following: CO₂ rebreathing, sedatives, ethyl chloride spray to the neck, amyl nitrite inhalation, intramuscular apomorphine, Largactil, quinidine, methedrine, phrenic nerve block or avulsion, and hypnosis. Under anaesthesia, treatment has included hyperventilation, use of muscle relaxants, use of a sudden blast of ether vapour, deepening anaesthesia, vagal block by the surgeon beneath the diaphragm, and the use of edrophonium⁴. However, the recent use of intravenous methylphenidate has produced promising results as reported by Macris and associates⁶. This study was undertaken in an effort to corroborate their findings.

METHODS AND MATERIALS

Methylphenidate hydrochloride (Ritalin®) is a central nervous system stimulant whose chemical structure is related to the piperidine compounds⁷. It is used to overcome fatigue, lethargy, and depression⁴. It is also reported to have properties resembling those of sedative drugs, i.e., controlling convulsions and diminishing tremors of Parkinsonism, as well as being of value in stopping shivering under hypothermia⁷. Its use as a barbiturate antagonist has been reported also⁸.

Twenty-two cases of hiccup during operation were collected in a 10-month period. All operations were done under general anaesthesia except one, in which the patient was awake and had local anaesthesia (see Tables I and II). One case of hiccups occurred during induction, 20 cases during maintenance, and one in the awake patient who had local anaesthesia. When hiccuping occurred, 14 patients were given an intravenous dose of 10 mg of methylphenidate and 8 patients were given a 20-mg dose. The length of time for injection was about 30 seconds.

RESULTS

In 12 cases hiccup stopped during injection, in seven cases it stopped within 45 seconds, and in three cases it stopped within 3 minutes. In two cases, hiccup recurred, necessitating an additional dose, but in a third case, hiccup responded briefly to repeated doses and finally persisted until the end of the case. In each of these three cases, the initial dose was 10 mg. The average length of time between recurrence was 45 minutes. In each of the eight cases in which a dose of 20 mg was used, hiccup stopped during the injection. In 14 of the cases under general anaesthesia several other methods to stop hiccup were tried first, for periods ranging up to 20 minutes, without success. When intravenous methylphenidate was given, the hiccup stopped.

TABLE I
ANESTHETIC AGENT -

Balanced (nitrous oxide, narcotic, and muscle relaxant)	13
Methoxyflurane	4
Halothane	3
Innovar (fentanyl-droperidol)	1
Local	1
	22

TABLE II
SITE OF OPERATION

Upper abdominal	8
Lower abdominal	8
Extremities	2
Other sites	4
	22

A transient rise in blood pressure, an average of 10 mm Hg was observed in 11 cases and a transient rise in heart rate of no more than 10 beats per minute was observed in five cases, but both blood pressure and heart rate returned to pre-injection levels within 5 to 7 minutes. No respiratory disturbances were noted. No patients showed any evidence of awakening after injection of the drug.

DISCUSSION AND CONCLUSION

In 22 cases of hiccup in which intravenous methylphenidate was used as an initial or final means of treatment, hiccup stopped in every case. It recurred in three cases, two of which responded to a subsequent dose. The duration of the action of a single dose appeared to be approximately 45 minutes. In the third case, methylphenidate was abandoned after it became apparent that its effect was evanescent. Doses of 10 mg had been used in these three cases, this may mean that a dose of this magnitude was barely effective. The 20-mg dose was more effective because it stopped hiccup during injection of the drug *each* of the eight times it was used.

In 13 of the 22 cases, "balanced" anaesthesia was used (nitrous oxide, narcotic, and muscle relaxant). With this type of anaesthesia proportionately more muscle relaxant might be used than narcotics, sensory reflex activity might be left relatively undepressed by too little narcotic and thus make hiccup more likely to occur.

Hiccup can be regarded as a reflex response to vagal stimulation of the partially anaesthetized respiratory centres and incompletely paralysed peripheral musculature.⁴ The following is postulated as a mechanism of action of methylphenidate.

It is proposed that there is a "zone of irritability" of the respiratory centres (in the case of hiccup, the inspiratory centre specifically) in which the centre, being in a partially anaesthetized state, is being bombarded with stimuli from

the operative field. The centre responds erratically with an abbreviated inspiration which is manifested as hiccup. The respiratory centre is thus involved in a cycle with the phrenic centre and the rest of the reflex arc.

In order to arrest hiccup, a block in this chain of events must be imposed, in this case, perhaps at the respiratory centre. Under anaesthesia, the activity of the centre may be shifted away from the "zone of irritability" by either deepening or lightening the anaesthesia. At a deeper level of anaesthesia, the respiratory centre, being more depressed, will fail to respond to stimuli, while at a lighter level, the respiratory centre, being less depressed, will respond more readily to stimuli. Its response, however, in this less depressed state will be more fully integrated so that, when an attempt at inspiration is made, a normal full inspiration will result instead of an abnormally abbreviated one. Thus, hiccup will tend to occur less as the activity of the centre shifts in either direction away from the "irritable zone." Methylphenidate may shift the respiratory centre to a less depressed state, breaking the chain of events that results in hiccup.

This hypothesis applies to the awake patient, the level of wakefulness of the respiratory centre might be further elevated by administration of the drug. In the anaesthetized patient the respiratory centre receives stimuli from the operative field, but in the awake patient the centre receives them from the region of the underlying disorder. Even in the awake patient the drug might shift the level of wakefulness of the respiratory centre away from the "zone of irritability" and break the chain in a similar manner.

SUMMARY

The causes and treatments of hiccup are discussed. Twenty-two cases of hiccup occurring under anaesthesia are reviewed in which intravenous methylphenidate was used as treatment. Hiccup stopped in every case, recurred in three, and persisted in one. Twenty milligrams of methylphenidate administered intravenously was the most effective dose. A mechanism of action of the drug is postulated.

RÉSUMÉ

Au cours de l'anesthésie, le hoquet cause habituellement des ennuis au chirurgien. Il faut distinguer le hoquet de l'effort que fait le malade pour tousser lorsqu'il a un tube dans la trachée.

Nous avons essayé plusieurs traitements préconisés antérieurement, mais aucun ne nous a donné satisfaction. Récemment, le phénidate de méthyl a été suggéré. L'étude que nous avons faite confirme l'efficacité de cette substance dans le traitement du hoquet, nous avons obtenu promptement des résultats positifs dans 22 cas consécutifs. Chez trois malades, le hoquet est réapparu, mais, après avoir répété l'injection, il est disparu chez deux malades.

La dose optimale semble être de 20 mg, administrée par voie endoveineuse, en 20 secondes. Il est possible d'observer une hausse temporaire de la pression sanguine. Nous n'avons pas observé d'autres effets secondaires.

Nous avons émis une opinion sur le mécanisme d'action de cet agent.

REFERENCES

- 1 SAMUELS, L Hiccup—A Ten Year Review of Anatomy, Etiology and Treatment *Canad M A J* 67 315 (1952)
- 2 BUTT, H R, HAMELBERG, W, & JACOBY, J Hiccup. Its Possible Causes and Treatment in Anesthesia *Anesth & Analg* 40 181 (1961).
- 3 CECIL, R L & LOEB, R E A Textbook of Medicine, 11th ed Philadelphia W B Saunders, Co (1963)
- 4 WYLIE, W D & CHURCHILL-DAVIDSON, H G A Practice of Anesthesia Chicago Year Book Medical Publishers, Inc (1962)
- 5 GOODMAN, L S & GILMAN, A The Pharmacological Basis of Therapeutics, 2nd ed New York The Macmillan Co (1955)
- 6 MACRIS, S G, MACRIS, G J, CACOURI, A N, & KARAPIPERIS, S N Intravenous Methylphenidate for the Treatment of Singultus *Anesth & Analg* 42 440 (1963)
- 7 BORTOLUZZI, E, ROELLA, C, BORTOLUZZI, S, & MONTOLI, E Methylphenidate in the Treatment of Shivering *Anesth & Analg* 42 325 (1963)
- 8 O'RIORDON, E & MARCUS, P Barbiturate Antagonists *Anesth & Analg* 40 188 (1961)