THE PHARMACOLOGICAL ACTIONS OF PARENTERALLY ADMINISTERED MAGNESIUM SALTS. A REVIEW

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THE depressant action of parenterally administered magnesium salts in animals (1, 2, 3, 4, 5, 6, 7) has naturally led to various attempts to apply this action therapeutically in man. For example, it was introduced by Blake in the treatment of tetanus (8, 9) and by Peck and Meltzer (10) as a general anesthetic. Curtis, Gwathmey and others used it in conjunction with other anesthetics (11, 12, 13, 14, 15, 16, 17, 18), while various workers in obstetrical clinics, following Lazard and Alton and Lincoln, having recommended its use as an anticonvulsant in eclampsia (19, 20, 21, 22, 23, 24, 25, 26, 27). Blackfan and others have employed it in relieving the convulsions of nephritis (28, 29, 30, 31), while Yaskin has recently reported on its use in the metrazol treatment of schizophrenia (32). The present review is devoted principally to an analysis of the pharmacological action of magnesium. An analysis of the principles underlying its action should make clear the limitations and advantages to be expected from the practical use of magnesium salts in clinical therapeutics.

I. THE PHARMACOLOGICAL ACTION OF MAGNESIUM

(*A*) *Absorption and Excretion of Magnesium*

Magnesium salts are absorbed to a limited extent from the gastrointestinal tract (33, 34), the usual effect of magnesium sulfate by mouth being purgation without increase in serum magnesium (35). In the presence of advanced renal damage, however, some increase in serum magnesium has been reported following oral administration (36). Injected magnesium is distributed at first through the extracellular fluid alone (37), but subsequently part is temporarily stored elsewhere in the body (33). Ultimately it is excreted almost entirely in the urine, as was first shown by Mendel and Benedict (33, 38, 39), with no increase of stool magnesium and no purgation (35). Excretion is quite rapid at first, but requires some days before it is complete. In subjects with renal damage the rate of excretion is much reduced (31), being roughly proportional to the impairment of glomerular filtration.

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(B) *Effects of Magnesium on the Nervous System*

The effects of magnesium on the nervous system are closely related to the momentary concentration of magnesium in serum (4, 40, 41). In animals the earliest effect is retardation of peripheral neuromuscular transmission (4, 44). At serum concentrations of about 10 m.eq. per liter muscles fail to respond to single shocks and to slow tetanic stimulation, while they continue to respond to fast tetanic stimulation after the concentration has risen far higher, e.g., at serum concentration of 30 m.eq. per liter tetani of 200 per minute produce a response. Reflexes disappear at differing concentrations of serum magnesium, depending on the natural frequency of discharge of the efferent part of the arc. Thus tendon reflexes, being simple twitches, disappear at 10 m.eq. per liter; respirations, depending on tetani of 40 per second, disappear at 15 to 20 m.eq. per liter; while the corneal reflex, which depends on tetani of 200 per second, does not disappear until concentrations of 30 to 35 m.eq. per liter are attained. These actions of magnesium on the nervous system are to a large extent obviated by the presence of an excess of calcium (42).

Experiments on man prove that magnesium has an action on the central nervous system as well as an effect on neuromuscular transmission. Peck and Meltzer (10) observed that magnesium sulfate injected intravenously into patients reduced sensitivity to pain and dulled consciousness, so that at slightly higher concentrations the patients became so completely unconscious that major surgical operations could be carried out. On recovery there was no memory of what had occurred during the period of apparent unconsciousness. This is unequivocal evidence that magnesium does act on the central nervous system (5, 6), and so by analogy it may be argued that the apparent narcosis in animals may not be due wholly to neuromuscular paralysis. Unfortunately, from the practical standpoint, unconsciousness and cessation of spontaneous respiration occur at about the same concentration, i.e. at about 15 m.eq. per liter. It is, therefore, impracticable to use magnesium as a general anesthetic unless artificial respiration is supplied as well. Magnesium is dangerous; much more so than, for example, the barbiturates. Thus the ratio of lethal to effective dose, or "therapeutic ratio," is as high as three for sodium barbital injected subcutaneously in the rabbit, while it is only a little greater than unity for magnesium chloride similarly administered (43).

In the dog, however, it has not been proved that cessation of respiration and all other objective manifestations may not be due wholly to neuromuscular block rather than to central depression. Bryant, Lehmann and Knoefel (1) claim that spinal reflexes may disappear while motor nerve transmission is still intact. Their evidence is, however, unsatisfactory, since they omit description of the rate of stimulation of the motor nerve. On the other hand Matthews and Brooks in a crossed

circulation experiment (44) found that the respiratory center was still active at a concentration of magnesium sufficient to produce complete paralysis of skeletal muscle.

(C) *Effects of Magnesium on the Cardiovascular System*

Magnesium is a powerful vasodilator (3, 31, 45, 46). Amounts too small to affect demonstrably the nervous system will produce flushing, sweating, and an intense sensation of warmth in man (31). This effect is so regular and so striking that its appearance following the injection of magnesium into the antecubital vein has been used as a measure of circulation time (47). A fall in blood pressure does not usually accompany this initial cutaneous vasodilation. As somewhat larger amounts are injected the blood pressure is apt to decline. This decline is gradual in the anesthetized dog (3), and often dramatically sudden and severe in normal unanesthetized man (31). Hypertensive subjects frequently fail to respond with any fall in blood pressure; in those responding the decline is apt to be less precipitous than in normal individuals (31). The fall in blood pressure depends upon rate of injection as much as upon the amount injected, so that depressor effects may be more readily demonstrated with concentrated than with dilute solutions, and more readily with intravenous than with subcutaneous or intramuscular administration. The blood pressure tends to return to its normal level even while the concentration of magnesium in serum remains distinctly elevated.

The effect of magnesium on the heart has been the subject of several studies (7, 48, 49, 50). In general there is in the dog no demonstrable effect at concentrations less than 10 or 12 m.eq. per liter, except for some tachycardia and occasional minor changes of the T wave and the QRS complex (7). In man there is a slight initial bradycardia rather than a tachycardia (31). As the concentration rises above 15 m.eq. per liter the PR interval is lengthened and the QRS complex widens (7). This impairment of intracardiac conduction becomes more marked as the concentration rises, until the heart is arrested in diastole. In order to demonstrate these changes artificial respiration is usually necessary, since they all appear above the concentration at which spontaneous respiration fails. It may therefore be stated that magnesium has almost no effect on the normal heart at concentrations used in clinical practice. Intravenous magnesium has been recommended therapeutically in the treatment of paroxysmal tachycardia and other arrythmias associated with increased cardiac automaticity (50). On the basis of the evidence presented it is difficult to determine whether or not these pathological hearts were more responsive than normal.

(D) *Miscellaneous Effects of Magnesium*

Vomiting is occasionally noted in the dog (3, 33) and in man (31) during the intravenous injection of magnesium. In man it is usually

preceded by a sensation of intense thirst. The mechanism of this effect is not known, and may be due either to reflex or to central action. When it occurs, it is commonly associated with the initial acute fall in blood pressure.

(*E*) *Relation of Effects to Concentration of Magnesium in Serum*

In table 1 the various pharmacological actions of magnesium are summarized, together with the concentrations of magnesium in the serum usually associated with each effect.

TABLE 1

Effects of Parenteral Magnesium, and the Concentrations of Magnesium in Serum at Which They are Usually Manifest

Action	Magnesium of serum, m.eq. per liter
No apparent effects	2
Initial tachycardia (dogs)	2–5
Initial bradycardia (man)	2–5
Initial fall in blood pressure (dogs)	2–5
Flushing, sweating, sensation of heat	2–5
Vomiting	2–10
Progressive fall in blood pressure	5+
Beginning auriculo-ventricular block	10+
Failure of tendon reflexes	10+
Beginning intraventricular block	12+
Failure of respiration	15+
Failure of corneal reflex	30+
Cardiac arrest	30+

II. Use of Magnesium Intravenously in Man

Magnesium was long ago recommended in the treatment of convulsions of *tetanus* (8, 9). Since it inhibits neuromuscular transmission, its use for this purpose is entirely rational. It has also been tried as a *general anesthetic* for surgical operations (10). However, as has already been noted, respiratory paralysis appears at a concentration almost the same as that required to induce anesthesia, so that it is impractical to use magnesium alone as a general anesthetic. Advocates of its use, together with ether or other anesthetics (11, 12, 13, 14, 15, 16, 17), have failed to demonstrate any distinct advantage of such combinations (51, 52), while the danger of respiratory depression is probably increased. Intrathecally injected magnesium will produce *spinal anesthesia* (53), but the discovery of safer agents has prevented the extensive use of magnesium for this purpose. On the other hand magnesium intravenously is being used widely for the control of *convulsions*, in *acute nephritis* (28, 29, 30), in *chronic nephritis* (31), and in *eclampsia* (19, 20, 21, 22, 23, 24, 25, 26, 27). Since the vascular system is abnormal in all these conditions, it is quite possible that many of the beneficial effects which have been reported are due to its vasodilator action.

This seems especially likely because of the fall of blood pressure which sometimes accompanies clinical improvement, and because of the low concentrations which are sometimes effective. The characteristic depression of neuromuscular transmission, useful in the treatment of tetanus, may also play a role in controlling the convulsions associated with vascular disease. In spite of this uncertainty regarding the mode of action, there is good clinical evidence that magnesium intravenously is practically effective in controlling convulsions (29, 30, 31).

Recently the rapid intravenous injection of 20 to 30 cc. of 25 per cent magnesium sulfate has been recommended as an accompaniment of metrazol administration in schizophrenic patients (32). It was found that the convulsive seizures themselves could frequently be controlled without losing the therapeutic effect of the metrazol. Although successfully carried out over two hundred times, at least one fatality following the injection of 30 cc. has been reported (31). The use of such concentrated solutions intravenously is necessarily somewhat dangerous, and should probably be abandoned in favor of more dilute solutions (see below).

Magnesium has been given intravenously in the treatment of *paroxysmal tachycardia* (50) and of arrythmias due to hyperexcitable foci in the heart. It does tend to depress the rate of conduction in the heart, but the concentrations necessary to accomplish this end are usually sufficient to depress or arrest respirations as well. As has been stated above, it is of course possible that diseased hearts may be abnormally susceptible to the action of magnesium, but it seems somewhat doubtful whether the small doses recommended (50) have much effect on cardiac rhythm.

III. Mode of Administration and Precautions

Convulsions are probably at present the chief indication for the use of magnesium intravenously. Intramuscular injection may be substituted for intravenous, but it is more difficult by this route to maintain an effective yet safe concentration of circulating magnesium. The effects on the nervous system depend on the existing concentration of magnesium in the blood serum. Since it is easier to control the rate of injection of a dilute solution, maintenance of an effective concentration is facilitated and the degree of fall in blood pressure is more readily controlled. The report of a fatality following the rapid injection of concentrated magnesium sulfate solution has already been mentioned (31).

In the New Haven Hospital we have found an isotonic or slightly hypotonic solution of magnesium sulfate (about 2 per cent of the hydrated salt, $MgSO_4 \cdot 7H_2O$) both safe and effective in the control of convulsions (31). In adults about 500 cc. of this solution is injected intravenously during a period of thirty to sixty minutes. The blood pressure is followed at frequent intervals. Knee jerks and respiratory

rate are also observed closely. Any serious depression of respiration will be preceded by disappearance of the tendon reflexes, which are therefore a valuable guide in determining the rate of injection. Fall in blood pressure is to be expected, and in itself is not sufficient reason for stopping the injection. If the drop is alarming, the rate of injection should be diminished. Calcium chloride solution suitable for intravenous injection should always be immediately available. This will effectually antagonize respiratory depression, if it should appear. (If occasion should arise to inject the calcium chloride intravenously, the injection should be made very slowly in order to obviate the danger of sudden ventricular fibrillation due to the calcium (54, 55).) In patients with normal renal function the magnesium is largely excreted in the urine within four to eight hours, so that repeated injections may be required, and can be given with impunity. In patients with marked depression of renal clearances, on the other hand, the concentration of magnesium in the serum may remain elevated for several days (31). Therefore, although a second injection may be required, not more than a liter or so should be given within a twenty-four hour period, and subsequent injections must be given with caution.

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CIRCULAR LETTER TO SECRETARIES OF SPECIALTY BOARDS

According to a communication received by the Secretary of the American Board of Anesthesiology, Inc., under date of April 4, 1942, from the Secretary of the Advisory Board for Medical Specialties, Major Seeley of the Procurement and Assignment Service communicated with the latter secretary that the Advisory Board for Medical Specialties' combined recent requests called for 3,200 specialists between the ages of 37 to 45. He asks that all men known to be qualified be canvassed and that those between the ages of 37 to 45 be encouraged to make immediate application for the type of service they desire. Major Seeley mentioned that among the specialists particularly desired many will be needed for Anesthesiology. He also calls attention to the recent announcement in the *Journal* of the American Medical Association of March 28, 1942, page 1146, and asks the Advisory Board for Medical Specialities for assistance in the stimulation of applications of qualified individuals to fill these vacancies.