

Conclusion. Combinations of amidopyrin with magnesium chlorid in experimental animals exhibit antipyretic synergism, and, to a lesser extent, diminished toxicity.

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Influence of Magnesium Salts Upon the Toxicity and Antipyretic Action of the Salicylates.

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In the preceding paper we have shown that magnesium chlorid is antipyretic to rabbits in hay-infusion fever. Furthermore the antipyretic efficiency of amidopyrin was found considerably potentiated by combination with magnesium chlorid, although in the same combination the toxicity appears slightly decreased.

The synergistic action of magnesium combined with antipyretic drugs is further illustrated by the following experiments upon magnesium combinations with salicylates. The work will be described under 3 heads: (1) toxicity in normal mice of sodium salicylate alone and in combination with $MgCl_2$; (2) antipyretic action in fevered rabbits of sodium salicylate alone and combined with $MgCl_2$; (3) antipyretic action in fevered dogs of aspirin alone and in combination with magnesium oxide.

1. Toxicity.

In normal white mice, the m.l.d. (minimal lethal dose) of sodium salicylate was found to be about 600 mg. per kilo (Table I). Similarly, the m.l.d. of a combination of 2 parts sodium salicylate with 3 parts magnesium chlorid (anhydrous) was found to be approximately 975 mg. per kilo (Table II). Our criterion for judging the m.l.d., as will be seen, does not include an occasional fatality within that range of dosage where survival is obviously the rule.

In the previous report, it was shown that the m.l.d. for magnesium chlorid is approximately 1.05 gm. per kilo. Thus the predicted m.l.d. for the present combination with sodium salicylate would be 807.5* mg. per kilo. Inasmuch as 975 mg. were, with 1 exception, actually required, there is evidently an antagonism between the 2 drugs favorable to survival. The combination is about

* For prediction formula see other paper.

TABLE I. *Toxicity in Normal White Mice.*

Drug*	Mg. per kilo	Number of mice	
		Survived	Died
Sodium salicylate	550	5	1
	600	6	2
	650	2	2
	700	0	1
	1,000	0	2
	1,200	0	2
	1,400	0	2
	1,600	0	2
Sodium salicylate + MgCl ₂ (2:3)	875	3	0
	900	5	1
	925	3	0
	975	0	2
	1,025	0	2
	1,050	2	1

* 1% solutions.

20% less toxic than predicted. This accords with the mutual antagonism shown between many depressant drugs when combined, and is most readily explained by the wider distribution of the *loci* of toxic action.

2. *Antipyretic Action in Rabbits.*

In a series of 11 rabbits, the average temperature reduction resulting from the subcutaneous injection of sodium salicylate (in 5% solution) in doses of 100 mg. per kilo, amounted to 0.7° F. in 2 hours, and 1.0° in 4 hours. These effects are illustrated in Fig. 1, where the average curve is compared with the antipyretic curves resulting from 2 different mixtures of sodium salicylate (5%) and magnesium chlorid (5%).

The above amount of sodium salicylate was combined in 8 rabbits with magnesium chloride 150 mg. per kilo (ineffective alone). The temperature fell so rapidly that the former 2-hour level of 0.7° F. was attained during the first half hour. Sodium salicylate alone had practically no effect within that period. At the end of 2 hours, the average temperature was still about half a degree below that produced by the salicylate alone, but by the fourth hour, the magnesium effect wearing off, the temperature had begun to return to normal so that the position of the 2 curves nearly coincided.

Even when only 50 mg. per kilo of sodium salicylate were given with magnesium chlorid 150 mg. per kilo rapid reduction in temperature was noted. This combination was found more efficient in 13 rabbits, than 100 mg. per kilo sodium salicylate alone, for a period of over one and one-half hours. By the fourth hour, however, the temperature had returned practically to the original febrile level.

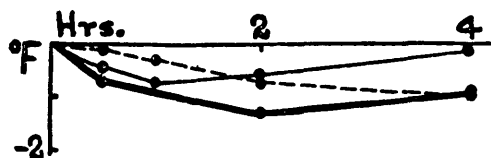


FIG. 1. Effects in febrile rabbits of subcutaneous administration of sodium salicylate alone and with magnesium chlorid, upon body temperature.

Abcissae, time after administration of antipyretic.

Ordinates, temperature changes °F., not absolute but calculated as difference from control febrile rabbits. Seventeen fever controls.

Dosage per kilo: Broken line, Na salicylate 100 mg. (average of 11 rabbits). Light continuous line, Na salicylate 50 mg. plus $MgCl_2$ 150 mg. (av. 13 rabbits). Heavy continuous line, Na salicylate 100 mg. plus $MgCl_2$ 150 mg. (av. 8 rabbits).

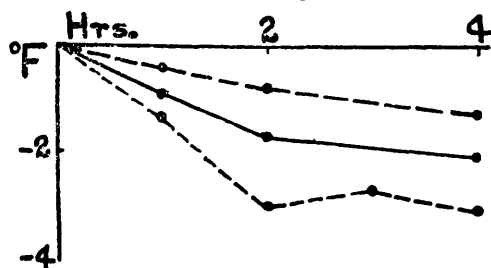


FIG. 2. Effects in febrile dogs of oral administration of aspirin alone and with magnesium chlorid. No fever controls. The temperature decreases are absolute rather than relative.

Dosage per kilo: Upper broken line, aspirin 100 mg. (1 dog). Lower broken line, aspirin 200 mg. (av. 2 dogs). Continuous line, aspirin 100 mg. plus $MgCl_2$ 150 mg. (av. 4 dogs).

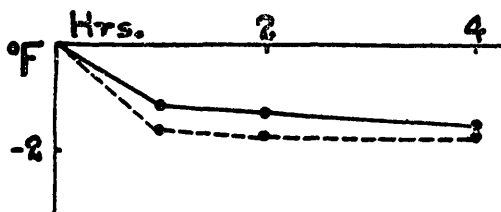


FIG. 3. Effects in febrile dogs of oral administration of aspirin alone and with magnesium oxid. Four fever controls.

Dosage per kilo: Broken line, aspirin 150 mg. (av. 4 dogs). Continuous line, aspirin 100 mg. plus MgO 100 mg. (av. 5 dogs).

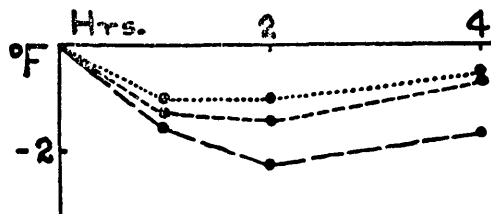


FIG. 4. Effects in febrile dogs of oral administration of magnesium oxid. One fever control.

Dosage per kilo: Dotted line, MgO 75 mg. (1 dog). Short dash line, MgO 150 mg. (1 dog). Long dash line, MgO 300 mg. (1 dog).

The slow, long-continued temperature fall produced by salicylate is thus shown to be modified to a more rapid though briefer effect when magnesium chlorid is added. It is significant that amounts of magnesium chlorid below the antipyretic threshold are sufficient to cause such a modification even when the salicylate dose is cut in half. Thus marked synergism outlasts the first hour. The crossing of the curves after a certain time is analogous to that noted with amidopyrin-magnesium antipyresis and definitely indicates that magnesium salts potentiate the early effects of antipyretic drugs, even when intense or prolonged action tends to be inhibited.

3. *Antipyretic Action of Aspirin and Magnesium by Mouth in Dogs.*

Aspirin administered by mouth† to fasting, fevered dogs in doses of 100 and 200 mg. per kilo, gave respective decreases in temperature of 1.3° (1 dog) and 3.1° F. (2 dogs) at the end of 4 hours (Fig. 2). The curve of antipyresis resulting from a combination of aspirin 100 mg. per kilo plus magnesium chlorid 150 mg. per kilo (4 dogs), occupies an almost exactly intermediate position. The combination thus accomplished the same result as would require about 150 mg. per kilo of aspirin alone.

Further experimental series were performed, using magnesium oxide in heavy suspension instead of the chlorid. In substituting magnesium oxide for magnesium chlorid, the dose used was reduced by one-third, giving a slightly higher molecular concentration of magnesium. As seen in Fig. 3, this combination (100 mg. of each drug) was not as effective as 150 mg. per kilo of aspirin alone, although presumably better than would be obtained by 100 mg. per kilo. The effect of the combination for the first 2 hours was slightly better than that produced by 150 mg. per kilo magnesium oxid alone, and did not show the remission seen 4 hours after the latter. (See Fig. 4, which shows the effects of 3 different doses of magnesium oxide.)

The weaker action of magnesium oxide as compared with the chlorid may be ascribed to slower absorption.

Conclusions. 1. Magnesium salts in mice appear to reduce the toxicity of salicylates (protective antagonism).

2. Magnesium augments the antipyretic action of sodium salicylate and of aspirin. When given subcutaneously with salicylate to fevered rabbits, the earlier stages of antipyresis are characterized by marked synergism.

† Suspended in about 200 cc. H₂O with or without acacia.