NITRITE TOLERATION

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Toleration of the vasodilator action of nitroglycerin occurs rapidly, may develop to a marked degree and is of exceedingly short duration. Stewart (1) has reported several instances of pronounced toleration of this drug, one individual for example failing to respond after six months use of nitrogelycerin to 500 times the initially effective dose. Workers in plants manufacturing explosives furnish examples of marked toleration of nitroglycerin, handling the substance without discomfort and working in an atmosphere that causes immediate throbbing headache in one unaccustomed to it (2). Toleration toward nitrogelycerin is further remarkable for its short duration. This is well illustrated by the custom of a worker in explosives placing a small amount of nitrogelycerin in the sweat-band of his hat when planning to be absent from work for a few days, in order to avoid the disagreeable symptoms resulting from a loss of considerable degree of tolerance, on return to work (2).

Inorganic nitrite, considered to act by a mechanism similar to that of nitroglycerin in causing vascular relaxation, is reputed to be incapable of causing a development of tolerance. The opinion of Matthew (3) in regard to this point has been accepted, as follows: " . . . . with sodium and potassium nitrites. I did not find any tendency to a toleration being established."

McGregor (4) has reported an indirect method of recording blood pressure that promised to be suitable to the need of frequently repeated registrations of blood pressure in a study of nitrite response. A standard clinical type of sphygomanometer is utilized in McGregor's method. Readings correlate closely with those obtained by the direct method. Animals accustomed

to the procedure may be used for frequently repeated registrations of blood pressure with an avoidance of the disturbing factors associated with a use of the direct method.

RESPONSE TO SODIUM NITRITE AFTER REPEATED ADMINISTRATION

The minimal effective intravenous dose of sodium nitrite for a rabbit was found to be 1.5 mgm. per kilogram. Ten full-grown rabbits gave reductions in blood pressure of 4 to 12 mm. of mercury, averaging 7 mm. with this dose. No response was obtained

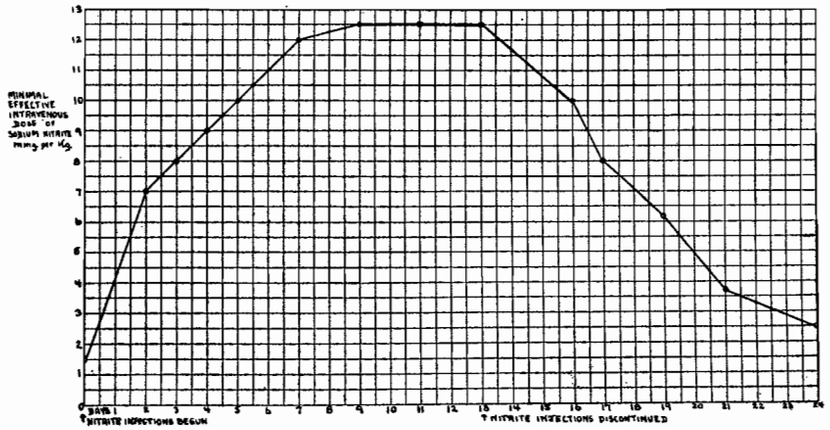

FIG. 1. DEVELOPMENT OF TOLERATION TOWARD SODIUM NITRITE RECOVERY OF SUSCEPTIBILITY ON WITHDRAWAL OF THE NITRITE

with 1.0 mgm. doses of nitrite. Injections were given at a uniform slow rate in each instance.

An attempt to establish tolerance toward sodium nitrite was made by injecting the drug subcutaneously, three times daily, in 8 full-grown rabbits. The dose of nitrite the first day was 5 mgm. per kilogram. This amount was increased each day by 5 mgm. until 3 doses of 30 mgm. per kilogram were given on the sixth to thirteenth days. Injections ceased on the thirteenth day.

The minimal effective intravenous dose of sodium nitrite was determined at intervals of two or three days in each of the 8 rabbits. A period of approximately eighteen hours was allowed to elapse following a subcutaneous injection before testing

the response to intravenous administration of the drug. Readings were made at two-minute intervals, utilizing the indirect method of recording described by McGregor.

Figure 1 shows the rapid decrease in susceptibility to sodium nitrate developing in the 8 rabbits. Response in the several animals proved to be remarkably uniform, with no material individual variations from the average curve shown in figure 1. Toleration of the nitrite ceased to develope further, shortly

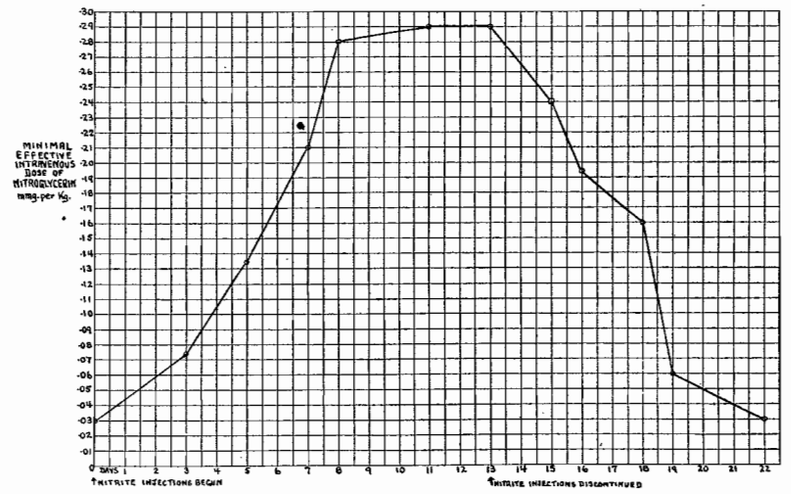

FIG. 2. DEVELOPMENT OF TOLERATION TOWARD NITROGLYCERIN IN RABBITS RECEIVING SODIUM NITRITE WITH RECOVERY OF SUSCEPTIBILITY ON WITHDRAWAL OF THE NITRITE

following the cessation of daily increment in dosage, indicated in the plateau existing from the ninth to thirteenth days of injection, in the curve of figure 1. Recovery of susceptibility to nitrite, following the cessation of injections of the drug, was nearly as rapid as the rate of development of tolerance, as shown in the curve.

RESPONSE TO NITROGLYCERIN IN RABBITS TOLERANT TOWARD NITRITE

The minimal effective intravenous dose of nitrogelycerin for the rabbit is 0.03 mgm. per kilogram. This dose in 4 full-grown rab-

bits gave reductions in blood pressure of 5 to 10 mm. of mercury, averaging 8 mm. Hypodermic tablets of nitroglycerin were found to be unreliable in attempting to obtain quantitative response. A freshly prepared dilution of the official spirit of nitroglycerin with 9 parts of 50 per cent alcohol gave consistent results and was used for determination of susceptibility. It was never necessary to inject more than 1 cc. of this solution. Double the quantity of 50 per cent alcohol, injected at the same rate at which all injections were made, caused no appreciable alteration in blood pressure.

The response to nitroglycerin was recorded in 6 full-grown rabbits injected with sodium nitrite three times each day in dosage described in the fore-part of this paper. Figure 2 shows the rapid loss in susceptibility to nitroglycerin occurring in the rabbits receiving sodium nitrite. There is an impressive similarity in the two figures in the rate and degree of loss of susceptibility, in the limitation of development of tolerance following cessation in further increase in nitrite dosage, also in the rate of recovery of susceptibility on withdrawal of nitrite.

CONCLUSION

1. Rabbits injected with sodium nitrite develop a tolerance of the vasodepressor action of that drug.

2. Cessation of increment in nitrite dosage results within a few days in cessation of further development of tolerance.

3. Recovery of susceptibility to nitrite quickly follows the withdrawal of nitrite administration.

4. Rabbits injected with sodium nitrite exhibit a tolerance toward nitroglycerin.

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