PHARMACOLOGY OF PLASMOQUINE WITH SPECIAL REFERENCE TO ITS ACTION IN PREGNANCY.

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Plasmoquine was prepared by Schulemann and his colleagues in 1924 and became available for general clinical use in 1926. Soon after its introduction into therapeutics it attracted considerable attention and a very large number of papers were published in succeeding years describing the clinical use of plasmoquine. Experimental studies on this new antimalarial drug were, however, remarkably few and a complete account of its pharmacological action was lacking. The author (1936) has already reported the principal pharmacological actions of this important drug. The toxicity tests on dogs, cats and rabbits agreed with those reported by Le Heux and Wijngaarden (1929). In guinea-pigs the dose which killed 50 per cent of the population after oral administration was found to be in the neighbourhood of 20 mg. per kg. The action of the drug on protozoa and bacteria was, however, not marked, e.g. a concentration as high as 1–1000 was required to inhibit the growth of *B. coli* or *B. pestis*.

The antipyretic action of plasmoquine was studied in rabbits with *B. coli* fever. It was found that smaller doses of plasmoquine (3 mg. per kg.) did not lower the temperature. Toxic doses of the order of 10 mg. per kg., however, reduced the normal as well as the fever temperature. Although smaller doses of plasmoquine did not by themselves reduce the fever temperature, it was found that in combination with quinine such doses reduced the temperature quicker than did quinine alone.

The R.B.C. count or the hæmoglobin percentage was not affected by administration of therapeutic doses (1 mg. per kg.) of plasmoquine in guinea-pigs. The fragility of the animal as well as human R.B.Cs. was unaffected by comparatively larger doses of the drug. The important action on the blood was that of methæmoglobin formation and the lowest concentration of plasmoquine that led to a definite formation of methæmoglobin detected spectroscopically was about 1 in 10,000.

The cardiovascular system was markedly affected by this drug. Intravenous injections of therapeutic doses (1 mg. per kg.) of plasmoquine produced a transient fall in blood pressure with rapid recovery in cats and dogs. Larger doses (2 mg. per kg.) produced a considerable fall in blood pressure accompanied by an irregularity of the heart. This irregularity was studied electrocardiographically and it was found that the normal action of the pace-marker was completely upset and most of the ventricular contractions were abnormal.

The digestive system was also found to be considerably affected by the drug. Movements of the gastro-intestinal tract were studied in animals with a gastric fistula and were found to be inhibited by larger doses of plasmoquine. Similarly acute experiments in intact animals and also experiments with isolated gut showed that plasmoquine inhibited gastro-intestinal motility. The important action, however, appeared to be on the liver and in a large number of experiments toxic doses (15 to 20 mg. per kg.) of plasmoquine administered orally or hypodermically were found to produce a fatty degeneration of the liver in guinea-pigs.

The action of plasmoquine on the central nervous system was studied by introducing the drug into the cerebro-spinal fluid of the Cisterna magna of dogs and cats. Such administration produced a marked depression of the vasomotor and respiratory centres.

The action of plasmoquine on the female reproductive organs was studied in detail so as to see how it would influence the course of a normal pregnancy. The effects on the animal uteri *in vivo* and *in vitro* were therefore studied. Cats, dogs, rabbits and guinea-pigs were used for the purpose and both the pregnant as well as the non-pregnant uteri were experimented upon. On the isolated uterus, plasmoquine was found to produce a slight contraction of the uterus in low concentration such as 1 in 300,000. Higher concentrations of the order of 1 in 100,000 or more, however, produced the opposite effect, viz. a relaxation and this was true for the pregnant as well as the non-pregnant uteri.

In intact animals, the uteri of cats and rabbits were found to be more susceptible to the action of plasmoquine than those of dogs. In cats a dose of 1 mg. per kg. usually produced a slight contraction of the uterus, while in dogs a dose of about 1·5 to 2 mg. per kg. was required to produce the same effect. Pregnant uteri of these animals responded to plasmoquine in the same way as did the non-pregnant ones. Although plasmoquine contracts the isolated and the intact uterus in low concentrations, it has the remarkable property of counteracting the effects of other uterine stimulants such as quinine or pituitrine. Thus, on the isolated rabbit's uterus a 1 in 500,000 dilution of plasmoquine produced a stimulant effect as did a 1 in 100,000 of quinine. A combination of the two, however, failed to produce any demonstrable effect on the tone or movements of an isolated rabbit's uterus. Similar but less marked inhibitory action was also seen in the intact uterus of experimental animals.

In order to get an idea of the response of the human uterus to plasmoquine, experiments were made on fresh strips of human uterus, in the same way as on the animal uteri. For this purpose strips from both pregnant and non-pregnant human uteri were obtained and suspended in warm oxygenated Locke's solution. The response, both in the gravid and the non-gravid uteri, was similar, although the gravid uterus was more sensitive to the drug. The nature of response of the human uterus was similar to that of animal uteri, low concentrations causing a contraction and higher ones a relaxation of the

uterine muscle. These observations were reported by the author in 1937. As the isolated human uterus responded to plasmoquine in the same way as did the isolated animal uteri, the response of the intact human uterus should also be similar to that of the intact animal uteri. The action of plasmoquine on the intact animal uteri is referred to above. In those experiments, however, the animal was under the influence of a general anæsthetic. Experiments were therefore made to see the effect of plasmoquine on the uterine movements of animals without administering any anæsthetic. Reynold's (1930) technique was followed for the purpose. With aseptic precautions a vaginal fistula was made in rabbits in such a way that the two uterine openings were pointing outside through the vaginal cuff, which was sutured to the anterior abdominal wall. The animal was allowed to completely recover from the operation and after complete recovery a small balloon was inserted into one of the horns, filled with water and connected to a Marey's tambour. Continuous tracings could thus be obtained and the effects of a therapeutic course of plasmoquine, given over a period of five days or more, could be recorded graphically. Such experiments showed that a single intravenous injection of a small dose (1 mg. per kg.) of plasmoquine produced only a slight transitory contraction of the uterus, while a therapeutic course of plasmoquine (0·5 mg. per kg.) given orally over a period of five days did not in any way affect the normal contractions of the uterine muscle during the course of treatment or some days after cessation of administration of the drug. The drug given in therapeutic doses orally, therefore, did not seem to modify the normal contractions of the uterine muscle.

Finally, to see if plasmoquine affected the normal course of pregnancy toxic as well as therapeutic doses of the drug were given to pregnant guinea-pigs which were in various stages of pregnancy. Toxic doses of the order of 15 to 20 mg. per kg. produced death of the fœtus along with the death of the mother. The death occurred from 2 to 7 days after administration of the drug and showed that even high concentrations of plasmoquine circulating into the blood did not produce sufficient action on the uterine muscle so as to induce an abortion.

The effect of therapeutic doses of plasmoquine was similarly studied in guinea-pigs. A dose of 0·5 mg. per kg. was administered orally to 12 guinea-pigs in various stages of pregnancy. None of these showed any signs of premature delivery and all delivered a normal litter in due course.

Discussion.

The experimental data given above shows that plasmoquine is liable to affect most of the systems of the body especially the cardio-vascular and the digestive systems. The cardiac irregularities are produced by intravenous injection of the drug and therefore this method of administration should be avoided. The liver seems to be the organ which is very often affected by toxic doses of the drug and it is likely that some of the toxic symptoms seen

after clinical use of the drug may originate in that organ. The action on the reproductive system, however, appears not to be harmful and there is some evidence to believe that even large doses fail to interrupt the course of a normal pregnancy. The fact that a combination of quinine and plasmoquine antagonizes the stimulant effect of each on the isolated uterus is interesting from a clinical point of view for such a combination has proved useful in the treatment of malaria.

Summary and Conclusions.

(1) Toxicity tests on protozoa and bacteria show that plasmoquine is not toxic to these.

(2) Plasmoquine has no antipyretic action of its own, but in combination with quinine it lowers temperature quicker than quinine alone.

(3) The cardio-vascular system is depressed by small doses of plasmoquine. Large doses produce a cardiac irregularity.

(4) The gastro-intestinal motility is depressed and toxic doses produce a fatty degeneration of the liver.

(5) The contractions of the isolated human or animal uterus are increased by low concentrations of plasmoquine and decreased by high ones.

(6) Contractions of the intact animal uterus are not affected by administration of therapeutic doses of plasmoquine given over a period of five days.

(7) Therapeutic or even toxic doses of plasmoquine given to pregnant guinea-pigs do not produce an abortion.

References.

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