Bromipin and its therapeutic importance / by Ludwig Hesse.

AUTHORISED TRANSLATION

FROM THE

"ALLGEMEINE MEDICINISCHE CENTRAL-ZEITUNG."

(No. 21—1900)

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BROMIPIN

And its Therapeutic Importance.

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During the latter part of the year 1898 the firm of E. Merck introduced under the name of "Bromipin" a new anti-epileptic and sedative. Several published communications relating to this medicinal agent show that, notwithstanding the host of new articles of the kind, this preparation has created interest among medical practitioners and acquired a definite position as a remedy. Bromipin is a compound of bromine with sesame oil, in which the bromine is united with fat acids of the oil as an addition compound of a permanent character and, in its taste, affording no indication of the presence of bromine.

Bromipin is the type of liquid brominized fat compounds, which, according to H. Winternitz, possess the same physiological characters as the iodized fat compounds which I have described in another publication as being for the greater part capable of assimilation in the muscles, the liver, and the subcutaneous tissues. It is assumed that the therapeutic action of Bromipin is due to the circumstance that most of the bromine it contains is assimilated and, at the seat of deposition, is gradually liberated by the action of the alkaline blood and other juices. This elimination takes places very gradually, and bromine may consequently be detected in the urine much longer than after the administration of alkaline bromides. It is certainly deserving of notice from a pharmacological point of view that by means of Bromipin very considerable quantities of bromine can be introduced into the system that are not combined with alkali metals. It may, therefore, be assumed *a priori* that no deleterious accessory effects need be apprehended,

and that the bromine contained in Bromipin would be effectual in much smaller doses than in the ordinary alkaline salts of bromine. Bromipin is prepared in two forms :—

I. As 10 per cent. Bromipin.

This preparation is a pale yellow, viscid, oily liquid of 1·008 gravity at 20° C.; it is insoluble in water, but when shaken with water forms a white emulsion from which the Bromipin separates a heavy oil on standing for some length of time. In absolute alcohol Bromipin is also insoluble, but it dissolves in ether, benzene, chloroform, or petroleum spirit. When an ether solution is shaken with silver oxide or mercury oxide the presence of bromide cannot be detected. By boiling for half-an-hour with caustic potash or soda solution the oil is saponified and the bromine is separated from its combination with the fat acids. The aqueous solution acidified with nitric acid gives with silver nitrate the characteristic precipitate of silver bromide. Mixed with strong sulphuric acid, Bromipin evolves heat, and immediately turns brown, becoming rapidly darker coloured and more viscid, until at last it carbonizes and disengages sulphurous acid.

II. As 33.3 per cent. Bromipin.

This preparation is a thick viscid oil of pale brown colour, resembling in solubility the ten per cent. preparation, except that it dissolves more slowly on account of its greater consistency. The behaviour with re-agents is also similar. The specific gravity is 1·311 at 20° C. By reason of the thick consistency of this preparation it is not so convenient to take internally, and it should, therefore, be administered in capsules of 2 grammes contents.

Both the composition of Bromipin and its behaviour in the animal organism admit of the conclusion that in the extensive range of neurasthenia a very advantageous field for its application will be found. The observations of DORNBLÜTH are of interest in that respect (1). From the physiological behaviour of Bromipin he concludes that, in regard to its action in neurasthenia, it may

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(1).—Dr. O. DORNBLÜTH, "On Bromipin Merck."—*Aerztliche Monatsschrift.* 1899, II. Part 5.

differ from alkaline bromides, and on that ground he uses this preparation chiefly in the case of such nervous affections as are not at all or only partially influenced by bromine salts. Bromipin was found to be especially efficacious in relieving nervous palpitation of the heart at night time, which neurasthenic patients suffer from, and that symptom has ceased with repeated doses of a teaspoonful at night. In some instances the administration of Bromipin continued for a week has effected a permanent cessation of this very troublesome symptom. Equally satisfactory results were obtained by DORNBLÜTH in the treatment of excitable heart in neurasthenic patients, even in that condition when the slightest sensible impression, unexpected by the patient, produced long continued palpitation. In such cases DORNBLÜTH orders a tea-spoonful of Bromipin 2 or 3 times daily, while he was formerly in the habit of giving twice the quantity of bromine in the form of bromine salts in order to obtain only a temporary effect. In cases of neurasthenic anxiety DORNBLÜTH was highly satisfied with the use of Bromipin, and according to the experience of many other physicians it renders excellent service in all nervous disorders, especially of hysterical patients. In less serious cases of morbid excitement of the nervous system small doses are sufficiently effectual. This is especially the case with children, inasmuch as excitement of the nervous system arising from various causes, and even cramp may be readily relieved. In one case of convulsive tic, for which ordinary bromine compounds had proved ineffectual, administration of Bromipin was followed by considerable alleviation ; and in another case of trigeminal neuralgia that had long been unsuccessfully treated, SCIPIO LOSIO obtained permanent relief by the use of Bromipin (2).

WULFF employed Bromipin for the relief of nervous insomnia with very good results, and he also prescribed it for sea sickness, with the result that it was effectual as a preventive in the case of persons who were affected by the shortest sea passage (3). In one instance he gave doses of two capsules, containing each 2 grammes of 33·3 per cent. Bromipin every three hours for twelve hours

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(2).—Dr. SCIPIO LOSIO.—*Gazzetta* med. delle Marche, 1899. 142.

(3).—Dr. WULFF, "The action of Bromipin and its use in Sea Sickness."—*Aerztl. Monatsschrift*, II., 1899. Part II.

before starting, and in another he gave two capsules five times. To produce the preventive effect tolerably strong doses are therefore necessary. WULFF was equally successful in cases of sea sickness that had already commenced. At first he gave two or three tea-spoonfuls of ten per cent. Bromipin every two hours and, as the sickness abated, a smaller dose at longer interval. The effect was less rapid in such cases as showed prominently gastric symptoms, but by the addition of small doses of half a milligramme of atropine in those instances until the gastric symptoms ceased, he was enabled to obtain the desired result with comparatively small doses of Bromipin.

The question has still to be considered whether neurasthenic affections constituted the chief cases for the application of Bromipin as a remedial agent, or whether it may not come into still greater use in the treatment of epilepsy. In any case it is certain that the use of Bromipin is a great advance in the treatment of epilepsy. The first announcement of that view was made by Professor Dr. H. GESSLER, of Stuttgart (4). He described the effect of Bromipin upon a patient subject to frequent violent attacks who had been long unsuccessfully treated with adonis and sodium bromide. With a daily dose of three tea-spoonfuls of ten per cent. Bromipin, the attacks became less violent, and the patient remained for a considerable period free from attack. Subsequently Professor Dr. G. LEUBUSCHER, of Meiningen, took up the use of Bromipin (5)., and he describes it in his work as a valuable addition to the materia medica, having like GESSLER come to the conclusion that Bromipin is tolerated in such cases and produces good effects, where other bromine compounds fail. LEUBUSCHER gave epileptics two tea-spoonfuls three times daily, it was readily taken and the effects were very satisfactory in all instances. Disagreeable accessory effects were never observed. After administration of Bromipin for months there was no instance in which acne supervened, nor did any of the other

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(4).—Prof. Dr. H. GESSLER, "The Therapeutic action of Bromipin."—*Württemb. Medicin. Correspondenzblatt*, 1898. No. 46.

(5).—Prof. Dr. G. LEUBUSCHER, "Contributions to the knowledge and treatment of Epileptics."—*Monatsschrift für Psychiatrie & Neurologie*, 1899 V. Part 5.

symptoms of bromism affecting the stomach or intestines present themselves. At the meeting of physicians at Porta Westphalica on the 6th May, 1899, the use of Bromipin for lunatics was the subject of an interesting discussion. Dr. ZIMMERMANN (6)., of Hanover, stated that he had used Bromipin for ten patients mostly epileptic, in doses of from three tea-spoonfuls to three or four table-spoonfuls daily, in some instances for a short time only, and in most of the others for three or four months. Above all things he was impressed with the advantages of Bromipin by the absence of skin eruptions, and of catarrh of the stomach or intestines, which are so frequently consequences of the administration of bromine preparations. Professor Dr. CRAMER (7). reports as the result of his trials of Bromipin in the lunatic asylum at Göttingen, that it is equally as effectual as other bromine compounds such as potassium bromide without giving the patients any indication that they were taking a bromine preparation, which is a great advantage of Bromipin. Neither did he find it produce any kind of disagreeable accessory effects, more especially that he had never met with a case in which acne appeared as a result of the use of Bromipin.

The results of a very thorough investigation of the action of Bromipin were published by F. SCHULZE, based upon the observations carried out at the Göttingen Asylum (8). SCHULZE began with small doses of four grammes and gradually increased them until after fourteen days he gave eight grammes, and after another eight days ten grammes. That dose was continued for some length of time, and then he gave twelve grammes for fourteen days, then fifteen grammes for another fourteen days, again increasing the dose every eight days to twenty or twenty-four grammes, and in the case of one patient to as much as thirty and thirty-five grammes. Then the daily dose was reduced gradually to twenty-five, fifteen and ten grammes. His observations were made in reference to four male and two female patients,

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(6).—Dr. ZIMMERMANN, "On Bromipin."—*Allgemeine Zeitschrift für Psychiatrie*, 1899. Vol. 56.

(7).—Prof. Dr. CRAMER, "On Bromipin."—*Neurologisches Centralblatt*, 1899. No. 11.

(8).—Dr. F. SCHULZE, "Further observations on the action of Bromipin in Epilepsy."—*Göttingen*, 1899.

all of advanced age and bad cases. They had been previously accustomed to the administration of bromine preparations. In all instances the use of Bromipin was found to be unmistakeably attended with beneficial results in cases of epilepsy. With small doses of four to eight grammes SCHULZE certainly obtained only temporary effects, with medium doses of 10 to 15 grammes there was marked improvement, and with larger doses very distinctly favorable results. Even in the case of patients who had long suffered daily from violent attacks, the use of Bromipin had the effect of bringing about freedom from attack for intervals of as much as fourteen days. Meanwhile the mental condition of the patients was very much improved and the improvement maintained after reduction of the daily dose. The character of the attacks was also milder. SCHULZE infers from his very careful observations that Bromipin really has the capacity of counteracting epileptic seizures, and at the same time it has the effect of improving the general condition of patients who have suffered very considerably. Under treatment with Bromipin the acne nodules and pustules resulting from previous use of alkaline bromides disappeared, the appetite was good, and the digestion undisturbed. The formerly fœtid odour of the breath also disappeared.

Satisfactory results have also been obtained in Italy from the use of Bromipin in the treatment of epilepsy. SCIPIO LOSIO employed it in one case with very marked success, and he especially mentions that the preparation is well tolerated, while the general condition of the patients taking it is sensibly improved.

WULFF bears similar testimony to the efficacy of Bromipin in the treatment of epilepsy. In the case of one patient who was unable to take potassium or sodium bromides even in moderate doses, since both salts caused loss of appetite, depression, weariness with very great production of acne symptoms; even Erlenmeyer's bromide water in small doses had the same effects; but when Bromipin was given in small doses an astonishing improvement was effected in the course of a few weeks. The seizures became less frequent and less violent, and at the time of the publication of WULFF's work the patient had already been free from an attack for a period of seven weeks. The bromine

acne disappeared gradually and the general condition of the patient improved, especially the appetite. In the case of a child of eleven years with whom other treatment had been unsuccessful, WULFF also obtained very satisfactory results by the use of Bromipin.

DORNBLÜTH records similar experiences, and all these statements meet with confirmation from other sources. Reports issued from numerous hospitals agree in furnishing evidence that the frequency of the seizures is at least mitigated, they are less violent and pass off more quickly. The patients become more tranquil in every way, less irritable and more at ease. Moreover, it is generally agreed that the use of Bromipin, as compared with the use of other bromine preparations, does not produce any disagreeable accessory effects. Under the influence of treatment with Bromipin acne decreases, and in no instance has there been any manifestation of the symptoms of bromism. Numerous observers have, however, mentioned the beneficial influence exercised upon the general condition of patients, under treatment with Bromipin, with increase of body-weight and improved appearance. This latter result is, undoubtedly due to the very ready digestibility of sesame oil, to which Professor VON NOORDEN and DR. STÜVE have directed attention.

The circumstance that Bromipin does not disturb the stomach or bowels, even when taken for long periods, is, no doubt, explicable by the very ready assimilation of the brominized fat by the stomach. The quantity of alkaline bromide that may be formed, in consequence of reaction with the intestinal juice, is so minute that any disturbance of the bowels by so called "salt-action" appears to be out of the question. That circumstance is the more important in connection with the therapeutic use of Bromipin, because the treatment in such cases as are now referred to, frequently has to be continued for twelve months. The absence of bromine acne may be due to various causes. It may be that, as a result of the very gradual and progressive elimination of bromine from the brominized fat deposited in the body, a comparatively smaller quantity of bromine becomes therapeutically active at one time; or it may be that, in the absence of any disturbance of the stomach, the reflex irritation productive of acne pustules is not produced.

Bromipin, which has proved itself to be an excellent therapeutic agent, is very especially adapted for use in cases where the occurrence of the frequently serious symptoms ot bromism—whether disturbances of the central nervous system, affections of the digestive organs or cutaneous eruptions—have prevented further treatment with bromine salts. It is also to be recommended for patients who for some reason or other are disinclined to submit to treatment with bromides. SCHULZE confirms the previously expressed opinion that the bromine present in Bromipin possesses a greater degree of activity than that present in bromine salts or bromalin. His own experience supports that opinion. Some patients object to the oily taste of Bromipin, and in such instances it may either be mixed with a trace of peppermint oil, so stirred up with beer or given in capsules. The 33.3 per cent. Bromipin, in capsules, is especially adapted for such patients as object to the oily taste of the preparation and desire to have the largest amount of bromine. It is, however, considered by competent authorities, to be a very great advantage that Bromipin can be injected subcutaneously, and we are informed that extended observations in reference to the subcutaneous as well as rectal administration of Bromipin are now in progress. Bromipin is also absorbed to some extent when rubbed into the skin, but such a mode of administration is less promising.