ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN — POLONIA
VOL. XXXIII, 25 SECTIO D 1978

Zakład Neuroradiologii i Rentgenodiagnostyki. Instytut Radiologii. Wydział Lekarski.
Akademia Medyczna w Lublinie
Kierownik: prof. dr hab. Stanisław Bryc
Zakład Farmakologii. Instytut Patologii Klinicznej. Wydział Lekarski.
Akademia Medyczna w Lublinie
Kierownik: prof. dr hab. Zdzisław Kleinrok

Stanisław BRYC, Zdzisław KLEINROK,
Zdzisław BORZĘCKI

Trials of the Elimination of the Central Effects of Ronpacon Cerebral 280 after its Administration into the Cerebral Lateral Ventricle in Rats

Próba eliminacji ośrodkowych efektów Ronpacon Cerebral 280 po jego zastosowaniu do komory bocznej mózgu szczura

Испытание элиминации центральных эффектов Ронпакон Церебрал 280 после его применении в латеральный желудочек мозга крысы

The progress of X-ray diagnosis exerts an influence on medical treatment effects. The diagnosis of intracranial lesions poses clinical as well as radiological problems which often cannot be solved after careful consideration of information obtained by adequate diagnostic procedures. Cerebral pneumography plays a definite role in diagnosing intracranial tumours. It is considered that the air used in the pneumography, does not always show each part of cerebral ventricles. Also the air ventriculography which in a great deal of cases leads to proper surgical treatment does not bring thorough information about the essence of a tumour and its exact localisation.

Introduction of positive oil contrast ventriculography permits to have the seat of a tumour localized quite precisely, and sometimes to define the kind of pathological process. Administration of this positive contrast medium did not make the state of a patient worse, and there is no need to intervene surgically, what was sometimes an absolute necessity after the air injection. Unfortunately, post mortem examination showed inflammatory changes in arachnoidea in some of the patients (13). The oil

contrast medium may bring a discomfort to the patient due to the blocking of the aqueduct (8, 15). In this situation experiments are going on in the direction of finding notgaseous contast mediums which possess the properties of Lipiodol, but would be devoid of its ill effects, are still being made. The contrast medium which has been introduced to clinical purposes and which is derived of phenyl-ethyl-decylan (Pantopaque, Ethiodan, Myodil) has not brought the desirable effects either. It was not until the desirable qualities of such water-soluble contrast mediums as Conray 60 or Ronpacon Cerebral 280 had been observed in angiography that some authors used them into ventriculogprahy, first in experiments on animals and then introduced on patients (1, 3, 4, 6, 9, 10, 19). Unfortunately, some of the authors observed the occurrance of side effects taking the forms of clonic seizures (3, 6, 14, 18). These divergent data taken from literature and also serious neurological complications observed by certain authors, have made us consider this problem. Our aim is to determine the influence of some drugs upon the seizures brought about by intraventricular injection of Ronpacon Cerebral 280 produced by Cilag-Chemie.

MATERIAL AND METHOD

The experiments have been performed on 201 white rats of the Wistar strain of both sexes whose body weight ranges from 150 to 200 g. Ronpacon has been injected intraventriculary by means of the method described by Herman (7). The moderate, death causing dose (LD_{50}) has been marked by Litschfield and Wilcoxon method (12). Subsequently, 30 min. before the intraventricular injection of Ronpacon in the case of remaining animals, drugs such as Phenobarbital (Luminal Natrium — Polfa 5 mg/kg, 2,5 mg/kg and 1 mg/kg), Meprobamate (Meprobamate — Polfa 50 mg/kg, 5 mg/kg and 1 mg/kg), Oksazepam (Relanium — Polfa 0,5 mg/kg, 0,1 mg/kg and 0,05 mg/kg) have been introduced intraperitoneally. The animals have been watched for 2 hours from the moment of the injection of a contrast medium and at the same time the number of rats affected by seizures, in each experimental group, have been registered.

RESULTS

The LD_{50} of Ronpacon Cerebral 280, which has been administered intraventriculary, is 14 (13,3—14,7) µl per one rat. All the medicine applied here display a strong protective activity that is, their administration in advance prevents completely or to a great extent the occurrence of seizures. The strongest preventing activity is exerted by Meprobamate which prevents the spasm completely when applied in doses 25 mg/kg and decreased considerably their frequency of occurrence when applied in

doses of 5 mg/kg. Some weaker activity is displayed by Glutetimid when applied in doses of 2,5 mg/kg. Phenobarbital, when applied in doses of 1 mg/kg or 5 mg/kg, and finally Oksazepam applied in doses of 0,1 mg/kg or 0,5 mg/kg.

DISCUSSION

Each new contrast medium should fulfill 3 following conditions: 1) perfect opacity, 2) harmlessness, 3) possibly the less risk of further complications (15). The need of examinations with the help of the water-soluble contrast medium is brought about by the cases of hydrocephalus and by patients who are clinically suspected for having intraventricular or mid--line structures tumours (16). In stereotaxy the designation of certain anatomical structures is also of great importance (13). The view is generally taken that the use of the above mentioned contrast medium reduces, to a great extent occurrence of unpleasent vegetative reactions. While taking the radiographs. there is no need of changing the position of head. This treatment saves time and filming and a better visualisation of brain ventricles is obtained. At same time nothing prevents the additional administration of air if necessary. Pathological processes in the vicinity of temporal horns may not, however, be revealed, for these structures are supperimposed by a too homogeneous shading intensity (14). C a m p b e l l et al. (3) observed, however, the occurrence of generalized seizures in the case of 2 patients, following the administration of a water-soluble contrast medium into base cisterns. One of them had a strong headache above the eyeballs. By the end of the contrast medium injection he vomited. In the course of a histological examination of two dead patients no changes have been observed. P i k a z a et al. (15) observed the seizures in 5 cases out of 260 and in 2 cases the seizures were dangerous for lives of the patients. These seizures appeared within one hours time from the moment of contrast medium injection. The water-soluble contrast medium is absorbed, as a rule, in half an hour and it is already impossible to trace it in 20 minutes time (18). First, separate seizures have been observed to have place in the neck, there they next changed into opisthotonus. The slightest touch then caused rapid seizures in the legs and later on, the spasm were becoming generalized and similar to those which can be observed in case of tetanus or strychnine poisoning. A significant fact is that the patients examined retained their consciousness. In the course of the above mentioned seizures no positive influence of any drugs has been notified. Sometimes the seizures lasted up to 14 hours and ceased only after curare administration and in general anaesthesia. In the case

of one patient permanent anterograde amnesia remained. The coexistence of the glottis spasms and a temporary lack of breath have also been observed.

Heimburger et al. (6) pointed out in their experiments that seizures are supposed to occur if the concentration of an injected contrast medium into cisterna magna reaches 50% of its concentration in the brain ventricles. No side effects resulting in hydrocephalus from the brain tumours, have been observed. The absorbable water-soluble contrast medium does not get over to the cisterna magna and to the surface of brain cortex. Although Ronpacon was getting over to the surface of the brain cortex, Szlaminski et al. (18) did not observed any negative effects. These authors had completed 15 ventriculography examinations using Ronpacon Cerebral 280 and did not find more serious side symptoms. Only in two patients has the nausea and vomitting been observed for a short time after 30 minutes from the injection of the contrast medium. They also did not find any changes in the cerebrospinal fluid and in the ependyme of the brain ventricle. Bryc (2) had completed ventriculography by means of Ronpacon Cerebral 280 on 45 patients with the tumours in the posterior cranial fossa. He also did not observed any side effects and the X-ray pictures presented a high diagnostic value. Żamojda et al. (20) did not notice any complications with 70 patients and the results of their examinations which had been carried out using Cerebral 280, were identical to the project data.

On account of obtaining valuable diagnostic data in ventriculography with Ronpacon Cerebral 280 produced by Cilag-Chemie, it is hard to stop these kind of examinations in spite of some hazard, which are not more frequent than those in case of the Conrady 60 application. It seems to the authors of the present paper that the experimental research upon animals they have carried out, in which the occurrence of seizures has been eliminated as a result of intraventricular injection of Ronpacon, is purposeful and justified. For it is know from the literature that the attempts of pharmacological control of the seizures already occurring with in human beings, do not produce desirable results. The early premedication by means of proper medicines would have been, to a great extent, practical value, namely in making the patient feel secure during his ventriculographic examination. It must be stressed here, that the results which have been obtained from the experiments on animals may apply to human beings only in some specified way (5).

REFERENCES

1. Bryc S., Latalski M.: Ann. Univ. M. Curie-Skłodowska, Lublin, Sectio D **19**, 17—20, 1964.
2. Bryc S.: Personal commun. 1976.
3. Campbell R. L., Campbell J. A., Heimburger R. F., Kalsbeck J. E., Mealey J.: Radiology 82, 286—289, 1964.
4. Davis F. M., Lewellyn R. C., Kirgis H. D.: Radiology **90**, 705—710, 1968.
5. Fischer D. E.: Radiologe **10**, 485—488, 1970.
6. Heimburger R. F., Kalsbeck J. E., Campbell R. L.: J. Neurol. Neurosurg. Psychiat. **29**, 281—290, 1966.
7. Herman Z. S.: Psychopharmacologia **16**, 369—374, 1970.
8. Horwitz N. M.: J. Neurosurg. **13**, 300—311, 1956.
9. Kandel E. J., Plewako N. S.: Wopr. Neurochir. **30**, 42—45, 1966.
10. Kleinrok Z., Bryc S., Borzęcki Z.: Pol. Tyg. Lek. **21**, 793—795, 1973.
11. Knoetgen J., Schwarz G., Argyropolos G.: Fortschr. Röntgenstr. **116**, 751—755, 1972.
12. Litschfield J. T., Wilcoxon F.: J. Pharmacol. Exp. Therap. **96**, 99—113, 1949.
13. Marcovich A. W., Walker A. E., Jessico C. M.: JAMA **116**, 2247—2254, 1941.
14. Picaza J. A., Hunter S. A., Cannon B. W.: J. Neurosurg. **33**, 297—303, 1970.
15. Picaza J. A., Hunter S. A., Lee L.: J. Neurosurg. **39**, 474—480, 1972.
16. Pradat P., Aboulker J., David M.: Neurochirurgie **13**, 157—175, Paris 1967.
17. Raimond A. J., Samuelson G. H., Yarzagaray L.: Radiology **94**, 714—717, 1970.
18. Szlamiński Z., Niezabitowski K., Wysocki R.: Przegl. Lek. **25**, 530—534, 1969.
19. Vinas F. J., Barrioneuevo P. J., Dujovny M.: Am. J. Roentgenol. **101**, 141—146, 1967.
20. Żamojda B., Łebkowski J., Lewko J., Ponikarczyk R.: II Ogólnopolskie Sympozjum Neurochirurgów. Augustów 1970.

Otrzymano 19 XI 1976.

STRESZCZENIE

W doświadczeniach przeprowadzonych na białych szczurach stwierdzono, że Ronpacon Cerebral 280 stosowany do komory bocznej mózgu szczura wywołuje drgawki, a w większych dawkach śmierć zwierząt. LD_{50} tego preparatu po jego zastosowaniu do komory bocznej mózgu wynosi 14 (13,3—14,7) µl/szczura. Uprzednie dootrzewnowe zastosowanie meprobamatu (0,1; 1 i 5 mg/kg), diazepamu (0,05; 0,1 i 0,5 mg/kg), glutetymidu (1; 2,5 i 5 mg/kg) lub fenobarbitalu (0,1; 1 i 5 mg/kg) wyraźnie, szczególnie w przypadku meprobamatu, zmniejsza występowanie toksycznych efektów Ronpaconu. Otrzymane wyniki mogą mieć praktyczne znaczenie w klinice w badaniach wentrykulograficznych.

РЕЗЮМЕ

В исследованиях проведенных на белых крысах доказано, что Ронпакон Церебрал 280 применяемый в латеральный желудочек мозга вызывает судороги в больших дозах даже смерть животных. LD_{50} этого препарата после его применения в латеральный желудочек становит 14 (13,3—14,7) μл/крысу. Предварительное внутрибрюшечное применение мепробамата (0,1, 1 и 5 мг/кг) диазепана (0,05, 0,1 и 0,5 мг/кг), глютетимида (1,0, 2,5 и 5,0 мг/кг) или фенобарбитала (0,1, 1,0 и 5,0 мг/кг) резко, особенно в случае мепробамата, понижало выступление токсических эффектов Ронпакона. Полученные результаты могут иметь практическое значение в клинике в вентрикулографических исследованиях.