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Effects of Carotid Artery Injections of some Roentgen Contrast Agents on the EEG in the Unanaesthetized Dog

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ABSTRACT

The effects of carotid artery injections of some roentgen contrast agents on the EEG have been studied in unanaesthetised dogs. The results support earlier clinical studies that the new contrast agent Ph DZ59B is suitable in carotid arteriography.

INTRODUCTION

Adverse effects of roentgen contrast media are most easily provoked and have the highest significance when the contrast media are injected into sensitive areas such as the cerebral circulation or the coronary circulation.

Numerous studies have been made on the circulatory effect in general of intracarotic injection of contrast media (7). Studies on the effects of intracarotic injection of contrast media on the EEG are relatively few. Foltz et al. (4) and Thomas et al. (6) reported the effects of injection of Diodrast on the EEG in both human subjects and monkeys and cats. The effects of carotid arteriography on the EEG in patients have been studied by Lundervold & Engeset (5) and recently by Binnie et al. (1).

The present investigation was undertaken to evaluate the effects of carotid artery injections of the methylglucamine salt (Ph DZ59B) and the sodium salt (Ph DZ59C) of a new contrast agent (Ph DZ59A) (Fig. 1) on the EEG in unanaesthetized dogs. At the same time, some limited tests of some other roentgen contrast agents were also made. The new contrast medium Ph DZ59B has been shown in other studies to cause fewer circulatory effects on intravascular injection than some other contrast media currently used (2, 3).

MATERIAL AND METHODS

Ten mongrel dogs weighing between 13 and 16 kg were used in the experiments. One week before the actual experiments, the dogs were prepared in the following way. Under penthotal anaesthesia and intubation with free respiration, the common carotid artery on one side was exposed through an incision in the ventro-lateral part of the neck. The exposed artery was punctured with the Seldinger technique and a radiopaque polyethylene catheter PE 160 was introduced into the internal carotid artery. The position of the catheter was checked by radiography (or TV-fluoroscopy) after a small injection of roentgen contrast medium. The catheter was fixed in a smooth curve with sutures to the soft tissues in the neck. With the aid of a special instrument, the catheter was tunnelled subcutaneously along the neck and the tip of the catheter drawn through the skin in the middle of the back between the scapulae. The tip of the catheter, fitted with a stopcock, was sutured to the skin with metal sutures. The catheter was kept open by intermittent flushing with saline containing a small amount of heparin. The catheter was protected by a canvas vest around the thorax and the neck of the dog. Usually the catheter remained patent in the artery for 2 weeks or longer. Occasionally, the catheter became occluded by kinking but could be straightened out with the metal guide wire. In two cases, the catheter slipped out of the artery, after 7 and 9 days respectively.

The EEG was recorded on an 8-channel Devices instrument (M 8 with EEG-amplifiers 7 C). The electrodes were Ag–AgCl-covered metal clips attached to the shaven skin and as a rule placed bilaterally over the frontal, parietal and occipital regions with a ground electrode in the midline of the neck.

Often only one pair of electrodes was used on the contralateral side. On the same recorder, a continuous electrocardiogram (usually lead 2) was also recorded. The paper speed used was 25 mm per second. After having sufficiently recorded the initial normal EEG and ECG patterns the recordings regularly started 30 sec before each injection and continued for at least 5 min after each injection. When changes were observed, continuous recordings were made for up to 10 min after the injection and

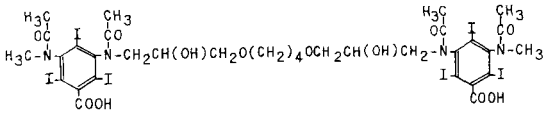

Fig. 1. Chemical structure of the new contrast agent in its acid form (Ph DZ 59A).

then intermittently at 10 min intervals as long as electroencephalographic changes were noted. Usually the recordings were discontinued 1 hour after the injection.

The dogs were kept under close observation during the recordings to detect eye movements, other muscular activity, or other events that may give artifacts on the electroencephalogram. The dogs were also kept under close clinical observation for 24 hours—particularly the dogs in which EEG changes had occurred.

In preliminary experiments, it was found that unanaesthetized dogs without muscle relaxantia accepted the experimental procedure well but the EEG-recording was partly obscured by muscle activity induced by the injections of contrast media. To avoid this, while still keeping the dogs unanaesthetized, Celocurin (1 mg/ml saline) was administered by an automatic injector at constant rate of 4–5 ml per min. When the muscles were fully relaxed an endotracheal tube was inserted and the dogs were maintained on artificial respiration. The respirator was adjusted so that the P_{CO_2} level was kept constant at the pre-Celocurine level during the entire experiment. The P_{CO_2} was measured at regular intervals during the experiment by means of a P_{CO_2} meter of electrode type (P_{CO_2} meter-IL, model 213).

When the P_{CO_2} attained a steady state and consequently no variations in the cerebral flow could be expected, different contrast media were injected through the catheter into the internal carotid artery. 24 series of injections were made in 10 dogs. Two dogs were used only once. In the other dogs more than one contrast agent was tested. All contrast agents were, with four exceptions, tested in more than one dog. An interval of at least 1 week between the experiments permitted any adverse effects of a contrast agent to disappear. The injection rate was kept constant at 5 ml per second, with a Contrac automatic injector. In each series of tests, volumes of 3 and 6 and 9 ml of a contrast medium were injected consecutively at intervals of 10 minutes in each animal. When EEG-changes occurred, no more injections were given during that experiment.

The following contrast media were tested.

1) Ph DZ 59 B (methylglucamine salt solution of Ph DZ 59A, Fig. 1, 235 mg I/ml)
2) Ph DZ 59B (methylglucamine salt solution of Ph DZ 59 A, 310 mg I/ml)
3) Ph DZ 59C (sodium salt solution of Ph DZ 59A, 310 mg I/ml)
4) Ph DZ 59C (sodium salt solution of Ph DZ 59A, 350 mg I/ml)
5) Angiografin (methylglucamine diatrozoate, Schering AG, Berlin; 310 mg I/ml)
6) Conray meglumine 282 (methylglucamine iothalamate, Mallinckrodt Chemical Works, St. Louis; 282 mg I/ml)
7) Isopaque cerebral (methylglucamine metrizoate and calcium metrizoate, Nyegaard & Co, Oslo; 280 mg I/ml)
8) Isopaque 350 (sodium metrizoate, calcium metrizoate and magnesium metrizoate, Nyegaard & Co, Oslo; 350 mg I/ml)
9) Methylglucamine metrizoate (235 mg I/ml)
10) Sodium metrizoate (310 mg I/ml)
11) Sodium metrizoate (350 mg I/ml)

RESULTS

1) *Ph DZ 59B 235 mg I/ml* was tested in 2 dogs with injections of 3 and 6 and 9 ml in each dog. No EEG changes occurred.
2) *Ph DZ 59B 310 mg I/ml* was tested in 3 dogs with injections of 3 and 6 and 9 ml in each dog. No EEG changes occurred.
3) *Ph DZ 59C 310 mg I/ml* was tested in 4 dogs with injections of 3 and 6 and 9 ml in each dog. In 3 of the dogs no EEG changes occurred. In one dog, EEG-changes occurred after 9 ml. However, in this dog P_{CO_2} varied considerably during the experiment, which may have led to changes in the cerebral circulation. This makes interpretation of the results in this dog difficult.
4) *Ph DZ 59C 350 mg I/ml* was tested in 2 dogs with injections of 3 and 6 and 9 ml in each dog. No EEG changes occurred.
5) *Angiografin 310 mg I/ml* was tested in 3 dogs with injections of 3 and 6 and 9 ml in each dog without EEG changes.
6) *Conray Meglumine 282 mg I/ml* was tested in 1 dog with 3 and 6 and 9 ml. No EEG changes occurred.
7) *Isopaque Cerebral 280 mg I/ml* was tested in 1 dog with 3 and 6 and 9 ml without EEG changes.
8) *Isopaque 350 mg I/ml* was tested in 3 dogs. In 1 dog, EEG changes occurred even after the 3 ml injection, in another after the 6 ml injection, and in the third dog after the 9 ml injection.
9) *Methylglucamine metrizoate 235 mg I/ml* was tested in 1 dog with injections of 3 and 6 and 9 ml without EEG changes.
10) *Sodium metrizoate 310 mg I/ml* was tested in 3 dogs. In 1 dog, EEG changes occurred after 6 ml and in one after 9 ml. In 1 dog, injections of 3 and 6 and 9 ml gave no EEG changes.
11) *Sodium metrizoate 350 mg I/ml* was tested in one dog with injections of 3 and 6 and 9 ml. After injection of 9 ml, EEG changes occurred.

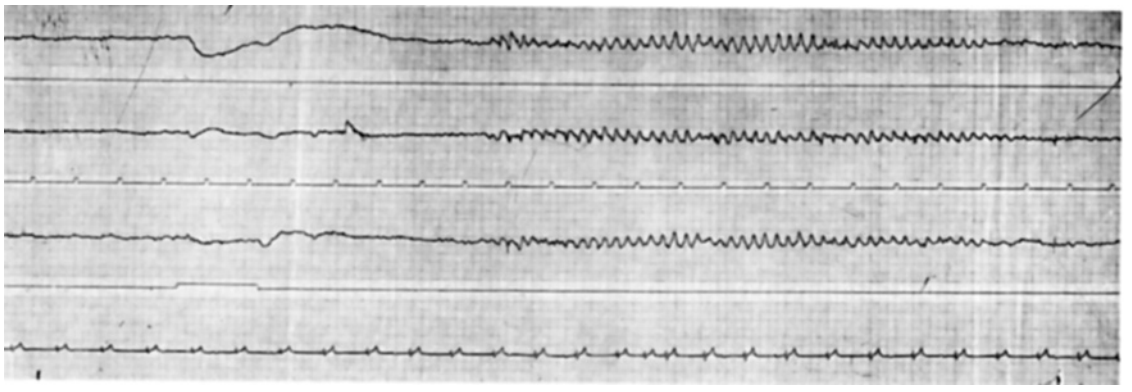

Fig. 2. EEG-changes after injection of a sodium metrizoate solution of very high concentration. *Upper trace:* Fronto-parietal ipsilateral EEG. *Second trace:* Indication of activity that may give artefacts: No artefacts were observed. *Third trace:* Parieto-occipital ipsilateral EEG. *Fourth trace:* Time in seconds. *Fifth trace:* Fronto-parietal contralateral EEG. *Sixth trace:* Injection marking. *Seventh trace:* ECG.

The pathological EEG-changes evoked by the injections of some of the contrast media having the highest concentrations were in most cases basically similar. 6–10 sec after the beginning of the injection, periods appeared with a bilateral rhythmic 3–4/sec activity of a partly paroxysmal type, often mixed with small sharp waves at the beginning of the periods (Fig. 2). Sometimes the EEG-change was a bilateral irregular spike and wave activity with a frequency of 5/sec (Fig. 3). The maximal peak-to-peak amplitudes during the abnormalities varied between different experiments (20–50 μV). Often the EEG-changes disappeared after 7–8 min but could persist for up to half an hour. These types of EEG--abnormalities were of an all or none type with or without the appearance of new wave forms. In one case a marked accentuation of a pre-injection periodic rhythm was observed. Bilateral transient flattening of the EEG was regularly seen immediately after the injection of the different contrast agents even when no abnormality with new wave forms was evoked.

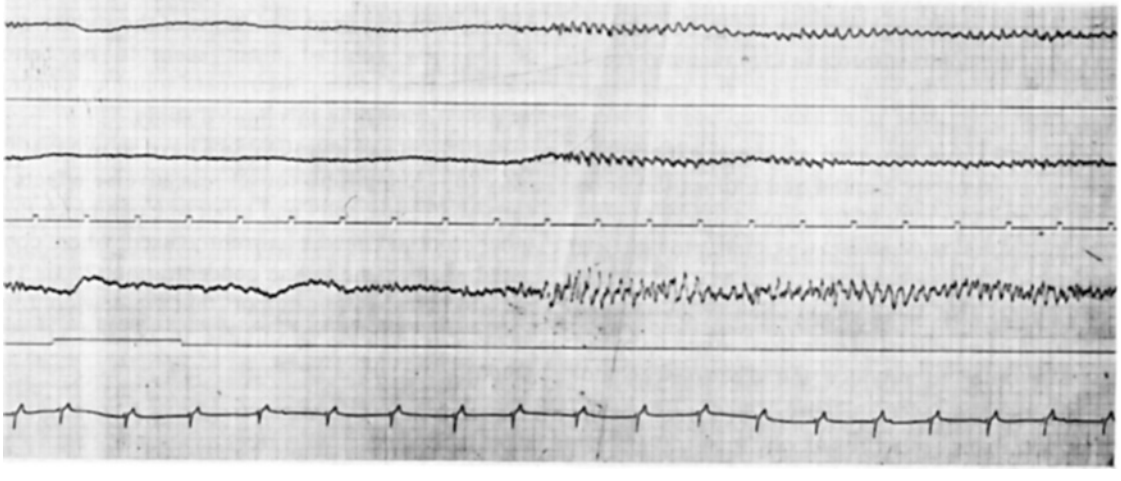

Fig. 3. EEG-changes after injection of a sodium metrizoate solution of very high concentration. The same registrations as in Fig. 2.

DISCUSSION

The Seldinger technique for introducing catheters into the exposed carotid artery in the dog proved to be very satisfactory. Bleeding around the catheter which occurs with cut-downs was totally avoided. There was no need to ligature the artery and the flow in the artery was unimpeded.

It is known that variations in P_{CO_2} may lead to considerable variations in the cerebral flow. However, the P_{CO_2} remained constant in all the experiments except in one where considerable variations occurred. In the other dogs, the circulatory state particularly in the brain was considered to have remained constant during the series of injections.

With one exception, the heart rate and the electrocardiogram remained unchanged during the experiments. The dog with ECG changes developed ventricular fibrillation 10 min after the last injection of contrast medium. The EEG was normal, however so the arrhythmia was probably caused by the succinylcholine. After about 10 min, the ventricular fibrillation ceased but during this period anoxic brain damage had occurred. The dog recovered during 24 hours. Although he regained his motor activity, he became blind. Postmortem examination failed to reveal any abnormality and the reason for the ventricular fibrillation occurring so late after the injection remains obscure.

When studying the effect of intra-arterial injection of contrast media and drugs it is very important to avoid changes in the cerebral circulation. If changes in the cerebral circulation occur during an experiment, considerable variations in the concentration of the contrast media in the brain may result in spite of using the same dose and the same injection rate.

The doses (ml/kg) used in these experiments were approximately 2 and 4 and 6 times the doses used in arteriography of the carotid artery in man. The injection rate (5 ml/sec) was similar to that used in man.

It appears that the concentration of anions and cations of the contrast agents must attain a certain level in order to produce the electroencephalographic changes seen in these studies. Low concentrations and low doses gave no reactions whereas higher concentrations and higher doses gave definite effects in the electroencephalogram in some of the tests. All the EEG changes were reversible and no permanent damage could be observed clinically to any of the dogs with one exception as stated above.

The methylglucamine salts of the contrast media tested produced no electroencephalographic changes in doses up to six times the clinical dose in carotid arteriography and with iodine concentrations up to 310 mg iodine per ml. Higher concentrations were not tested in this study. One reason for not increasing the iodine content of pure methylglucamine salt solutions is that the viscosity becomes too high for practical use in clinical radiography. However, the solutions tested here with iodine concentration around 300 mg of iodine per ml did not prove to be difficult to administer in these experiments. It is conceivable that the importance of viscosity in these connections has been overemphasized.

The present study support previous reports that the methylglucamine salts of the contrast agents are suitable in carotid angiography, provided the concentrations and doses are kept within reasonable limits.

A strict comparison of the anions of the different contrast agents is difficult from the present limited study but it appears that the anion of the new contrast compound Ph DZ 59A causes relatively little irritation to the brain. In this study the new contrast agent was investigated both in the form of the methylglucamine salt and the sodium salt at different concentrations in eleven series of injections. Only in one dog with varying P_{CO_2} EEG changes occurred. In this case the highest dose level (9 ml) of the sodium salt solution containing 310 mg I/ml was used. Solutions of the sodium salt of the new contrast agent seem to be better tolerated than sodium metrizoate solutions of similar iodine content in this limited study.

Earlier clinical investigations have shown that Ph DZ 59B (235 mg I/ml) causes less adverse effects in carotid arteriography and other angiographies than other contrast media currently used when compared at the same iodine concentration (2, 3). The present investigation support that the new contrast agent Ph DZ 59B is suitable in carotid arteriography.

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