

**ΦΑΡΜΑΚΕΥΤΙΚΗ.—The Role of Zinc Sulfate on the Systemic action of Cocain\*, by N. Klissiunis.**

It is well known that the addition of zinc salts [retards the absorption of many drugs which are parenterally injected, if for ex. zinc chlorid is added to Protamin insulin. There is also evidence that zinc salts injected together with adrenalin retards the absorption of the latter<sup>1</sup>. The same applies for the post. pituitary<sup>2</sup>, for folliculin<sup>3</sup> and thyrotropic extracts<sup>4</sup>.

From the literature available we could not find any experiments relative to the retardation of absorption of other drugs after the addition of  $\text{ZnSO}_4$ . A drug for which the physician does not wish a quick absorption in the human body is cocain. We have found in the literature, that the anesth. power of a cocain sol. could be increased through the addition of many drugs which chiefly retard its absorption. It was therefore interesting to test the systemic action of cocain in the presence of  $\text{ZnSO}_4$ . For this methods purpose we used cats of an average weight of 2–4 Kgs. In one group of 16 animals we have injected in the subc. back region a quantity of 0,03–0,04 g. of cocain hydrochloride per kilo of living weight.

This cocain we have dissolved in a quantity of water equal to 2 cc's per Kg. (Tabl. I). In another group of 24 animals we have injected the same quantity of cocain but with an addition of  $\text{ZnSO}_4$  in a quantity of 0,025–0,5 g. per kilo (Tabl. II). In an other series of experiments with cats we tried to equalize the osmotic and  $P_h$  differences of the cocain sol alone and the coc. sol. with  $\text{ZnSO}_4$ . For the preparation of isoosmotic solution we have used the cryoscopic method. Thus we found that a 2 % coc. sol. is osmotically equal to cocain 2 % + 7,5 %  $\text{ZnSO}_4$ , if we add to the control cocain sol. 1 % NaCl. These two solutions are isoosmotic and have a  $\Delta$  of approx.  $-76^\circ\text{C}$ . The  $P_h$  difference found were  $Ph=6$  for the cocain sol. and  $Ph=5,6$  for the cocain sol with  $\text{ZnSO}_4$ .

To bring them both to the neutral point we have dissolved the above mentioned substances in a buffer solution of 0,2/m of boric acid and 0,2/m Na-acetate in a proportion of 7 c. c. 0,2/m Na-acetate to 3 c. c. of 0,2/m Boric acid. Thus we obtained a 7,0  $Ph$  for the cocain sol. and 6,6 for the coc. sol. with  $\text{ZnSO}_4$ . The  $\Delta$  of these sol. was  $-1,48^\circ$  for the coc. sol. and  $-$

\* Ν. ΚΛΕΙΣΙΟΥΝΗΣ: Ἡ ἐπίδρασις τοῦ θειικοῦ ψευδαργύρου ἐπὶ τῶν γενικῶν ἐνεργειῶν τῆς κοκαΐνης.

1,39 - 1,39 for the coc. sol. with  $\text{ZnSO}_4$  which is sufficiently good for our experiments. The cats after injection were placed under observation in cages and notes were taken at short intervals for 3 - 4 hours. The epileptoid seizures in the tables I, II are valid for the period of 3 - 4 hours after injection. To determine the LD<sub>50</sub> of the buffered and isoosmotic solution of coc. and coc. with  $\text{ZnSO}_4$  we have made experiments in a third group of 58 cats with the buffered and isoosmotic solutions (Table III). The cats were placed in pairs and to each member of the pair one of the two solutions were injected. For the 2% coc. control sol. the quantities injected were equivalent to 0.03 - 0.045/Kg cocain and for the 2% coc. sol. with 7,5%  $\text{ZnSO}_4$  the quantities injected were equivalent to 0.03 - 0.07/kg cocain. The deaths were noted after 24 hours. On these findings we have calculated the LD<sub>50</sub> according to Kärber to be 0.035/kg for the coc. sol. and for the coc. sol. with  $\text{ZnSO}_4$  to be 0.058/kg.

As we can see from Table II by combining a dose of 0.04 - 0.05/kg  $\text{ZnSO}_4$  to the dose of 0.04 coc/kg. the seizures appear in 45' - 50'. We have no more seizures when the doses of  $\text{ZnSO}_4$  are increased to 0.15 - 0.5/kg. The life also of the cats is prolonged compared with the controls of table I. When an injection of 0.15g/Kg combined with 0.04g coc/Kg was made, in the form of a buffered and osmotically balanced sol., no seizures were observed and the mortality was lower. (Exp. 4, Tabl. I, II).

The description of an experiment on a pair of cats will make this clearer.

A - control cat: weight 2,2 kg. Injection of 2cc/kg from a 2% coc. sol., buffered and isoosmotic sol. (all times given are after injection) In 3' seizures were observed. 10 minutes later seizures were still observed but of a shorter duration. After 15' the seizures even shorter. The cat was lying in complete anesthesia on its side exactly the same condition was observed at 22' 30' 35'. At 40' after injection the seizures were less in number but of longer duration. 50' from the injection time a marked acceleration of respiration was observed. 60' later the cat is lying on its side and reacts on external irritation. The four legs show a tonic extension. At 90' it tries with head and legs to rise up and succeeds in rising the head, 100' after injection. At 130' it can uncompletely get up. At the 8th hour is lying on its side and shows abundant salivation. Periodical seizures are observed and finally it dies at 9 hours after injection.



B cat weight 2,5 kg. Injection of 2 cc/kg from a 2% coc. sol. with 7,5%  $\text{ZnSO}_4$  buffered and isoosmotic. At 15' it is restless and shows easy frightening. At 30' shows only a tremor of the head. At 45' it is sitting with four legs extended. The mild head tremor is continuing but it can move in its cage. At 55' it is sitting quietly extending its fore legs. At 80' starts crying. At 105' it is continually licking its legs and at 110' it can stand up. At 130' vomiting is observed and at 8 h. and 27 hours is sitting quietly and is running at times. 7 days after injection a small abscess was observed on its back. Afterwards no observations were made.

From Table III we can see that the LD<sub>50</sub> of coc.+ $\text{ZnSO}_4$  is greater than the LD<sub>50</sub> of coc. alone.

### CONCLUSIONS

The addition of 7,5% of  $\text{ZnSO}_4$  to a 2% coc. sol. delays the seizures, if they appear, prolongs life and diminishes mortality.

I thank Mss. Dosi very much for her technical assistance during these experiments.

TABLE I.

*Effect of subc. injections of cocain hydr. on convulsions and death rate of cats.*

No of exp.	Dosis of Coc. HCl.	No of cats		% mortality	Approx. time till death	Convuls. observed 3-4 h. after inj.	Average time till appearance of convuls.	% convulsions
		used	dead					
1	0.025	1	0	0	—	—	—	0
2	0.03	1	0	0	—	—	—	0
3	0.04	10	7	70	1h.-14 h.	++	4'-50'	100
4 <sup>1</sup>	0.04	4	4	100	25'-9 h.	++	2'-3'	100

<sup>1</sup> In this group with 0.04 Coc. HCl/kl the coc. sol was injected in a sol. of  $\Delta = 1.48$  and  $\text{Ph} = 6.8$ .

TABLE II.

*Protective effect of zinc sulfate in exper. convulsions induced in cats by coc. hydrochl. 1 kl subc.<sup>1</sup> 0,04 g.*

No of exp.	Dosis of zinc sulfate per kl.	No of cats		Percentage mortality	Appr. time to death	Seizures	Aver. time till appearance of convul.	Per % convulsive involvement
		used	dead					
1	0.04	1	—	—	—	1	45'	100
2	0.049	1	1	100	100'	1	50'	100
3	0.13	1	—	—	—	—	—	—
4 <sup>2</sup>	0.15	4	2	50	21h.-48h.	—	—	—
5	0.175	2	1	50	40h.	—	—	—
6	0.222	10	7	70	6h.-37h.	—	—	—
7	0.28 - 0.32	2	2	100	11h.-13h.	—	—	—
8	0.35 - 0.5	2	2	100	5h.-8h.	—	—	—

TABLE III.

## A. Cocain alone.

Number of cats used	Cocain per kil.	Number of deaths	
(1)	0.01	—	LD <sub>50</sub> after Kärber = 0.035/kil.
(5)	0.02	5 survive	
(6)	0.03	2 dead	
(6)	0.035	3 dead	
(4)	0.037	3 dead	
(5)	0.04	all dead	
(6)	0.045	all dead	

## B. Cocain with zinc sulfate.

(5)	0.035	all survive	LD <sub>50</sub> after Kärber = 0.058/kil.
(5)	0.04	3 dead	
(5)	0.05	2 dead	
(5)	0.06	3 dead	
(5)	0.07	all dead	

<sup>1</sup> In the exp 7-8 0.05 coc./Kl was injected.

<sup>2</sup> In the exp. 4 the coc. + ZnSO<sub>4</sub> was of an  $\Delta = 1.39^\circ$  and Ph = 6.6.

## ΠΕΡΙΛΗΨΙΣ

Εἶναι γνωστὸν ὅτι ἡ προσθήκη ψευδαργυρούχων ἀλάτων εἰς πολλὰ φάρμακα ἐπιβραδύνει τὴν ἀπορρόφησιν αὐτῶν. Διὰ τὴν κοκαΐνην δὲν ἀνεύρομεν σχετικὰ πειράματα ἐν τῇ βιβλιογραφίᾳ. Εἰς τὰ πειράματα ἡμῶν ἐχρησιμοποιήθησαν γαλαῖ βάρους 2 — 4 χιλ. Εἰς μίαν πρώτην σειρὰν πειραμάτων ἀπεδείχθη ὅτι ἡ ἔνεσις 0,04 γρ. κοκαΐνης κατὰ κιλὸν ἔχει ὡς ἄμεσον ἀποτέλεσμα ἐπιληπτοειδεῖς σπασμούς. Αἱ ἐνέργειαι αὗται ἐπιβραδύνονται καὶ ἐλαττοῦνται εἰς ἔντασιν, διὰ τῆς προσθήκης 0,15 γρ.  $ZnSO_4$  κατὰ κιλόν.

Πρὸς ἐξισορρόπησιν τῶν ὁσμωτικῶν διαφορῶν ὡς καὶ τῶν διαφορῶν εἰς πυκνότητα ἰόντων ὑδρογόνου τῶν δύο διαλυμάτων ἦτοι τῆς κοκαΐνης ἀφ' ἑνὸς καὶ τῆς κοκαΐνης μὲ  $ZnSO_4$  ἀφ' ἑτέρου, προσετέθη εἰς τὸ διάλυμα τῆς κοκαΐνης  $NaCl$ , ὥστε τὰ 2 διαλύματα κατέστησαν ἰσοοσμωτικά.

Διὰ τὴν ἐξίσωσιν τῶν διαφορῶν εἰς  $P_h$  διελύθησαν αἱ ὡς ἄνω οὐσίαι εἰς ρυθμιστικὸν διάλυμα  $M/0,2$  βορικοῦ ὀξέος καὶ  $M/0,2$  ὀξικοῦ νατρίου. Καὶ κατὰ τὴν ἔνεσιν τῶν διαλυμάτων τούτων παρετηρήθησαν αἱ αὐταὶ ὡς ἄνω διαφοραί.

Ἐκτὸς τούτου εἰς σειρὰν ἐξ 60 γαλῶν παρετηρήθη ὅτι ἡ θανατηφόρος δόσις διὰ 50 ζῶα ( $LD_{50}$ ) ἦτο ἀνωτέρα, κατὰ τὴν προσθήκην ψευδαργύρου εἰς τὸ διάλυμα.

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