PHARMACOLOGICAL EFFECTS OF CEFCLIDIN ON GASTROINTESTINAL TRACT, SECRETORY FUNCTION AND RENAL FUNCTION

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An examination of some general pharmacological effects of cefclidin (CFCL) and (CEZ) cefazolin had been made. A range of standard pharmacological tests were used to investigate effects on the gastrointerstinal tract, secretory function and renal function.

Local anaesthetic activity was also evaluated.

Some increase in the activity of gastrointestinal smooth muscle was observed following both CFCL and CEZ but there was no evidence of an effect on gastrointestinal conduction speed. Secretory function was not affected by CFCL, however, changes in gastric secretion, bile secretion and pancreatic output were observed after CEZ.

The highest does of CFCL caused an increase in urine volume and Na^+, K^+, and Cl^- excretion in rats. Whilst an increase in Na^+ was seen after CEZ no notable change in urine output was recorded. Glomerular filtration rates were not affected.

CFCL and CEZ were devoid of local anaesthetic activity.

Key words : cefclidin, general pharmacology, gastrointestinal, secretory and renal function.

Introduction

Cefclidin (CFCL) is a new parenteral cephalosporin synthesized by Eisai Co. Ltd, Japan. It has a broad antibacterial spectrum and potent activity against gram-negative bacteria including *Pseudomonas aeruginosa*. CFCL also showed high resistance to hydrolysis by and low affinity for various types of β-lactamases.

This paper describes the results of the pharmacological studies with CFCL in comparison with cefazolin (CEZ). CFCL and CEZ were each evaluated at two dose levels using a battery of standard laboratory tests designed to inverstigate the effect on the gastrointestinal tract, secretory function and renal function. Local anaesthetic activity were also inverstigated.

Materials and Methods

1. Materials

1) Animals

Male and female Swiss derived CD-1 mice (20 25 g), male Wistar rats (150 436 g), male Dunkin-Hartley guinea-pigs (312 382 g), and male and female beagle dogs (9.3 17 kg), were housed appropriately in air-conditioned temperature and humidity controlled rooms. The lighting schedule was 12:12 light/dark.

The animals were fed an appropriate laboratory diet. Tap water was available *ad libitum* except where otherwise indicated.

2) Test compounds

CFCL and CEZ were dissolved in physiological saline solution at different concentrations.

The other test materials used were cefazolin (CEZ) (Fujisawa Pharmaceutical Co., Ltd.), medicinal charcoal, lidocaine, inulin, p-aminohippuric acid (P.A.H.) (Sigma Chemical Co., Limited) : heparin (Evans Pharmaceuticals) chloralose (BDH Limited) : sodium thiopentone, sodium pentobarbitone (RMB Animal Health) : frusemide (Hoechst) : urethane (Aldrich Chemical Company Limited) mannitol (F.S.A. Laboratory Supplies) and

Table 1. Effects of intravenous administration of cefclidin and cefazolin on ionic concentrations, the volum of stomach contents, and gastric damage in the pylorus-ligated rat

(a) Expressed as mEq/vol

Group	Treatment	Dose (mg/kg) I.V.	Group mean value (±SD) for :					
			Volume (ml)	Na^+ (mEq/vol)	K^+ (mEq/vol)	Cl^- (mEq/vol)	H^+ (mEq/vol)	Gastric* damage
1	Vehicle (0.9% saline)	–	12.60 ±2.19	0.60 ±0.13	0.12 ±0.03	1.54 ±0.28	1.09 ±0.31	2.80 ±1.48
2	Cefclidin	300	11.80 ±2.27	0.56 ±0.12	0.11 ±0.02	1.40 ±0.31	1.00 ±0.33	2.70 ±1.70
3	Cefclidin	1000	10.40 ±2.42	0.53 ±0.17	0.08** ±0.04	1.30 ±0.35	0.81* ±0.21	3.50 ±1.65
4	Cefazolin	300	10.40 ±1.73	0.47* ±0.07	0.11 ±0.03	1.29 ±0.23	0.82* ±0.16	2.70 ±1.83
5	Cefazolin	1000	8.70** ±3.69	0.40** ±0.18	0.08** ±0.04	1.04** ±0.49	0.67** ±0.39	3.20 ±1.69

Significance of difference from vehicle-treated control groups using analysis of variance * : $p<0.05$ ** : $p<0.01$
Significance of difference from vehicle-treated groups using Kruskal-Wallis analysis of mean ranks

(b) Expressed as mEq/ml

Group	Treatment	Dose (mg/kg) I.V.	Group mean value (±SD) for :				
			Volume (ml)	Na^+ (mEq/ml)	K^+ (mEq/ml)	Cl^- (mEq/ml)	H^+ (mEq/ml)
1	Vehicle (0.9% saline)	–	12.60 ±2.19	0.049 ±0.013	0.010 ±0.022	0.122 ±0.007	0.085 ±0.013
2	Cefclidin	300	11.80 ±2.27	0.048 ±0.011	0.009 ±0.001	0.118 ±0.006	0.082 ±0.016
3	Cefclidin	1000	10.40 ±2.39	0.051 ±0.007	0.008 ±0.002	0.124 ±0.006	0.078 ±0.006
4	Cefazolin	300	10.40 ±1.73	0.045 ±0.005	0.010 ±0.002	0.124 ±0.006	0.079 ±0.008
5	Cefazolin	1000	8.70** ±3.69	0.045 ±0.009	0.009 ±0.002	0.113 ±0.021	0.070* ±0.021

Significance of difference from vehicle-treated control groups using analysis of variance * : $p<0.05$ ** : $p<0.01$
All groups consisted of 10 animals

sodium chloride (Animalcare Limited). The materials were dissolved in a medium compatible with the test procedure.

2. Methods

1) Effects on gastrointestinal motility in the mouse

Groups of 10 male mice were used in this experiment.

The method used was similar to that described by Takemori et al[1].

The mice were fasted overnight prior to the test but water was available *ad libitum*.

CFCL and CEZ (1,000 and 2,000 mg/kg) were formulated in saline administered intravenously into a tail vein.

Immediately after dosing each mouse received an oral dose of 0.25 ml of a 5% suspension of medicinal charcoal in water.

Exactly thirty minutes after dosing with charcoal the mice were sacrificed and the entire gastro-interstinal tract was quickly and carefully removed. The distance that the charcoal meal had travelled from the pyloric sphincter towards the caecum was measured and expressed as a percentage of the total intestinal length.

2) Effects on gastro-intestinal motility in the anaesthetised dog

Four female beagle dog were used in this experiment.

Prior to the commencement of the experiment, the dogs were deprived of food for a period of not less than 16 hours. Anaesthesia was induced by an intravenous injection of sodium thiopentone and maintained by intravenous α-chloralose (60 -80 mg/kg initially, and supplemented as required).

Catheters were introduced into a femoral artery and a cephalic vein to facilitate measurement of blood pressure and the administration of the test drugs and anaesthetic respectively. The femoral arterial cannula was connected to a saline/heparin (250 U/ml)-filled pressure transducer coupled to a chart recorder.

The trachea was cannulated to facilitate unimpeded respiration.

Two small saline-filled rubber balloons attached to catheter tubing were inserted into the stomach and lower small intestine via incisions made in the duodenum and upper ileum, respectively. The cannulae were coupled to appropriate pressure transducers and the contractions of the stomach and small intestine were recorded on the chart recorder throughout the experiment.

Table 2. Group mean percentage changes (± SD) in bile and pancreatic secretions (from mean pre-treatment or pre-dose values) following intravenous administration of vehicle or cefclidin

Treatment and dose	Time (minutes post-dose)	Group mean % change in output ± SD	
		Bile secretion	Pancreatic secretion
Vehicle 10 ml/kg	15	2 ± 5	6 ±42
	30	4 ± 7	9 ±51
	45	− 5 ±11	32 ±69
Cefclidin 500 mg/kg	15	5 ± 6	−14 ±13
	30	8 ± 9	− 0.4 ±20
	45	3 ± 4	−19 ±31

n=10

Table 3. Group mean percentage changes (± SD) in bile and pancreatic secretions (from mean pre-treatment or pre-dose values) following intravenous administration of vehicle or cefazolin

Treatment and dose	Time (minutes post-dose)	Group mean % change in output ± SD	
		Bile secretion	Pancreatic secretion
Vehicle 10 ml/kg	15	9 ± 8	21 ±53
	30	4 ± 8	27 ±85
	45	1 ±12	25 ±80
Cefazolin 500 mg/kg	15	139 ±30(n=9)	−24 ±36(n=9)
	30	164 ±43(n=9)	−16 ±38(n=9)
	45	139 ±49(n=9)	− 2 ±25(n=9)
	60	130 ±49(n=9)	8 ±45(n=9)

n=10, unless otherwise stated

Table 4. Effects of intravenous administration of cefclidin, cefazolin and frusemide on urine output in the rat

Group	Treatment	Dose (mg/kg i.v)	Mean total urine output at various intervals after drug administration (ml ± SD)					
			0−1 h	0−2 h	0−3 h	0−4 h	0−5 h	0−24 h
1	Vehicle	−	0.62 ±0.87	1.28 ±1.05	1.46 ±1.13	1.87 ±0.83	2.12 ±1.05	7.44 ±2.78
2	Cefclidin	300	1.10 ±0.65	1.38 ±0.64	1.44 ±0.71	1.73 ±0.83	1.91 ±0.92	6.52 ±2.99
3	Cefclidin	1000	2.32*** ±0.66	2.82** ±0.44	3.06** ±0.63	3.26** ±0.56	3.45** ±0.46	8.22 ±2.79
4	Cefazolin	300	0.42 ±0.46	0.85 ±0.48	1.36 ±0.30	1.60 ±0.31	1.66 ±0.27	8.00 ±3.44
5	Cefazolin	1000	1.26 ±0.74	1.62 ±0.86	2.00 ±0.88	2.56 ±1.27	2.72 ±1.45	7.84 ±3.04
6	Frusemide	2	4.22*** ±0.90	4.42*** ±0.88	4.52*** ±0.98	4.84*** ±0.98	4.92*** ±0.99	10.72* ±2.77

Significance of difference from vehicle-treated group using Kruskal-Wallis analysis of mean ranks
*: <0.05 **: <0.01 ***: <0.001

Once baseline levels had stabilised, vehicle, CFCL and CEZ were administered intravenously (5 ml/kg) with a minimum dose interval of 30 minutes.

3) Effects on gastric secretion

Groups of 10 male rats were used for this experiment which was performed essentially as described by Shay et al[2].

The animals were fasted for approximately 18 hours prior to pyloric-ligation. Water was available before pyloric-ligation but not during the experiment.

The rats were anaesthetised with ether and an incision was made in the abdomen. The duodenum was ligated 0.5 cm below the pyloric sphincter. Before the incision was sutured, 4 ml of warm 0.9% saline was injected into the abdominal cavity to minimise any stress effect.

Immediately after recovery from the anaesthetic the animals were intravenously dosed with either vehicle, CFCL or CEZ at a constant dose volume of 10 ml/kg.

Five hours after dosing, the animals were anaesthetised with ether and the stomach of each rat was carefully removed after clamping the oesophagus. The rat was then killed by cervical dislocation. The gastric contents were then analysed for H^+, Na^+, K^+ and Cl^- content using the following methods

H^+ pH meter titration

Na^+ Flame photometry

K^+ Flame photometry

Cl^+ Roche Cobas centrifugal analysis

Each stomach was opened along the greater curvature and examined macroscopically for damage in the glandular portion any damage was subjectively scored using the following scoring system

0 = normal

1 = slight hyperaemia

2 = marked hyperaemia

3 = haemorrhages

4 = small ulcers (1 mm)

5 = large ulcers (1 mm)

4) Effect on salivary secretion

Twelve male rats were used in this experiment. Each animal was anaesthetised with urethane (125 mg/100 g, i.p.). The trachea was cannulated to facilitate respiration. The carotid artery was cannulated to permit measurement of blood pressure using a heparin/saline-filled (250 U/ml) polyethylene catheter connected to a suitable pressure transducer and chart recorder. Heart rate was derived electronically from the blood pressure signal. The jugular vein was cannulated to facilitate intravenous administration of vehicle (10 ml/kg), CFCL and CEZ.

With the aid of a dissection microscope, one parotid duct in each animal was cannulated using polyethylene tubing of the widest possible internal diameter. Saliva produced was collected in calibrated micropipettes (10 μl).

Following a twenty-minute stabilisation period, vehicle (0.9% saline, 10 ml/kg) was administered intravenously. This was followed at approximately 20-minute intervals by CFCL and CEZ. The volume of saline secreted over the 20 minute post-dose collection period was recorded.

5) Effect on bile and pancreatic secretions

Groups of 10 male rats were used in this experiment.

Rats were anaesthetised with urethane (5 ml/kg of a 25% w/v solution, i.p.). The animals were maintained at 37°C on a heated table and the trachea was intubated to allow unimpeded respiration. A carotid artery and a jugular vein were cannulated to permit measurement of blood pressure and the administration of test drug respectively. The carotid arterial cannula was connected to a heparin/saline-filled (250 U/ml) pressure transducer, coupled with a suitable chart recorder. The heart rate was electonically derived from the pressure signal.

The bile duct was isolated at the point before entry into the pancreas and was cannulated at that point with polyethylene tubing of the widest possible diameter. The fluid was collected into calibrated 100 μl glass micropipettes (intraMARK^R) and the volume of bile secretion produced per 15-minute period was measured. A second polyethylene cannula was inserted into the pancreatic duct at the point of entry into the duodenum and the flow of pancreatic secretion was measured in 10μl glass micropipettes (intraMARK^R).

The basal flow rate from both cannulae was

measured for a minimum of 45 minutes (3 × 15 minute samples) prior to administration of treatment. Vehicle was then administered, followed by a single dose of CFCL or CEZ in each rat. The flow of bile and pancreatic secretions were measured at 15-minute intervals for at least 45 minutes after each dose.

6) Effect on urine and electrolyte

Groups of 5 male and 5 female rats were used in this experiment which was performed essentially as described by Lipschitz et al[3].

Approximately 18 hours before experimentation the animals were fasted.

On the test day water was removed and approximately 2 hours later vehicle, CFCL or CEZ was administered intravenously using a dose volume of 10.0 ml/kg. Immediately thereafter, each rat received 0.9% saline by oral gavage at a dose volume of 15 ml/kg and was placed in an individual metabolism cage. The urine was collected over the following 24 hours and the volume of urine excreted by each rat at 1, 2, 3, 4, 5 and 24 hours after test article administration was recorded. Urine collected during the first 5-hour period was analysed for Na^+, K^+ and Cl^- ions and the protein content using the following methods

Na^+ - Flame photometry

K^+ - Flame photometry

Cl^+ - Roche Cobas Centrifugal Anaylser using the BDH chloride reagent

Protein content Roche Cobas Centrifugal Analyser using the modified method of Macart and Gerbaut (Clin, Chim. Acta. 1984, Issue 141, 77)

7) Effect on renal function

Three female and one male beagle dogs were used in this experiment.

Anaesthesia was induced by an intravenous injection of sodium thipentone and maintained in anaesthersia by intravenoue α-chloralose (initially 40-50 mg/kg). The trachea was cannulated to facilitate breathing.

An incision was made in the lower abdomen and both ureters were cannulated close to their junctions with the bladder.

Both femoral veins and the right cephalic vein were cannulated for the administration of the infusates and test articles respectively.

A femoral artery was cannulated and connected to a heparin/saline-filled (250 U/ml) pressure

Table 5. Effects of intravenous administration of cefclidin, cefazolin and frusemide on the protein and electrolyte content of urine and collected for 5 hours after drug administration

Group	Treatment	Dose (mg/kg i.v)	Mean protein content of urine (mg/vol ± SD)	Mean electrolyte content of urine (mEq/vol ± SD)		
				Na^+	K^+	Cl^-
1	Vehicle	–	0.67 ±0.21	0.37 ±0.14	0.11 ±0.05	0.38 ±0.18
2	Cefclidin	300	0.80 ±0.34	0.45 ±0.22	0.10 ±0.04	0.44 ±0.22
3	Cefclidin	1000	1.69*** ±0.31	0.80*** ±0.11	0.17* ±0.03	0.82*** ±0.13
4	Cefazolin	300	0.64 ±0.16	0.37 ±0.09	0.07* ±0.02	0.32 ±0.08
5	Cefazolin	1000	0.92 ±0.43	0.62* ±0.25	0.08 ±0.03	0.36 ±0.18
6	Frusemide	2	0.50 ±0.26	0.66** ±0.10	0.12 ±0.05	0.65** ±0.12

Significance of difference from vehicle-treated group using Kruskal-Wallis analysis of mean ranks

*: <0.05 **: <0.01 ***: <0.001

transducer coupled to a suitable chart recorder. Heart rate was derived electronically from the blood pressure signal. Blood samples (5 ml) were obtained as required via the blood pressure cannula and placed into a heparin tube. The samples were centrifuged and the plasma removed and frozen.

Both femoral venous cannulae were connected to Sage Model 355 syringe pumps, and were set to deliver 0.9% sodium chloride at 0.25 ml/kg/minute and inulin/P.A.H./mannitol solution at a rate of 0.4 ml/minute throughout the experiment.

Sixty minutes following the commencement of the infusions blood and urine sample collections were commenced. Urine samples were collected over 20 minute periods and a blood sample was removed

Table 6. Assessment of the local anaesthetic activity of cefclidin and cefazolin using the guinea-pig corneal reflex

Group	Treatment	Concentration of test solution (% w/v)	No. of animals showing a complete (6/6) response to corneal stimulation at time (min) post-dose											
			5		10		15		20		25		30	
			L	R	L	R	L	R	L	R	L	R	L	R
1	Vehicle (0.9% saline)	–	5	5	5	5	5	5	5	5	5	5	5	5
2	Cefclidin	5	5	5	5	5	5	5	5	5	5	5	5	5
3	Cefclidin	10	5	5	5	5	5	5	5	5	5	5	5	5
4	Cefazolin	5	5	5	5	5	5	5	5	5	5	5	5	5
5	Cefazolin	10	5	5	5	5	5	5	5	5	5	5	5	5
6	Lidocaine	1	0**	5	0**	5	0**	5	3	5	5	5	5	5
7	Lidocaine	2	0**	5	0**	5	0**	5	1*	5	2	5	4	5

Significance of difference from vehicle-treated group using
Fisher' exact test * : $p<0.05$ ** : $p<0.01$

Table 7. Group mean response of guinea-pigs given intradermal injections of cefclidin, cefazolin and lidocaine

Group	Treatment	Dose (% w/v)	Pinprick response as % of control response at time (min) after injection :					
			5	10	15	20	25	30
1	Vehicle (0.9% saline)	–	100	100	100	100	100	100
2	Cefclidin	5	97	100	100	100	100	100
3	Cefclidin	10	97	100	100	100	100	100
4	Cafazolin	5	97	97	100	100	100	100
5	Cafazolin	10	100	100	100	100	100	100
6	Lidocaine	0.2	67*	60**	57**	60**	87	97
7	Lidocaine	0.4	3**	0**	0**	0**	30**	47**

Significance of difference from vehicle-treated group using
Fisher' exact test * : $p<0.05$ **: $p<0.01$

midway through each urine collection period. Vehicle, CFCL and CEZ were administered intravenously using an interdose interval of 60 minutes.

The rates of renal clearance for both inulin (Glomerular filtration route) and P.A.H. were calculated as follows

$$\text{Clearance} = \frac{U\,V}{P}$$

where U = concentration of either inulin or P.A. H. in the urine (mg/l)
V = volume of urine passed (ml/min)
P = concentration of either inulin or P.A. H. in the plasma (mg/l)

8) Local anaesthetic activity

i) Corneal reflex

Groups of five male guinea-pigs were used in this experiment which was performed essentially as described by Chance and Lobstein[4].

One drop (100 μl) of CFCL or CEZ was applied to the cornea of the left eye of each animal and an equal volume of vehicle administered to the contralateral eye. Control animals received vehicle (100 μl) in both eyes.

ii) Weal test

Five male guinea-pigs were used in the experiment which was performed according to the method of Bulbring and Wadja[5].

On the day prior to the experiment both flanks of each animal was depilated by shaving.

Intradermal injections of 0.1 ml of saline or test drug were made into the marked sites on the depilated flanks of the guinea-pigs. Each dilution of test preparation was tested in five guinea-pigs.

The pain response to six light pinpricks were determined at the site of drug application at intervals of 5 minutes for 30 minutes.

Results

1) Effects on gastrointestinal motility in the mouse.

Neither CFCL nor CEZ (1,000 and 2,000 mg/kg) caused any noteworthy effect on intestinal motility when compared with vehicle-treated mice.

2) Effects on gastrointestinal motility in the anaesthetised dog.

Motility of the stomach and small intestine were monitored in four anaesthetised female beagle dogs following intravenous administration of vehicle (5 ml/kg 0.9% saline), CEZ (300, 1,000 mg/kg) and CFCL (300, 1,000 mg/kg).

Stomach and intestinal motility were assessed as the mean amplitude of contractions over five-minute periods and by rate of contraction (min-1), averaged over five-minute periods also.

Intravenous administration of vehicle (5 ml/kg) did not exert any effect on either arterial blood pressure or gastro-intestinal motility.

Administration of CFCL at 1,000 mg/kg decreased stomach motility by up to 85% in all four animals. However, CFCL administered at 300 mg/kg induced an increase in size of contractions in one animal. No consistent effects on the rate of stomach contraction were observed following administration of CFCL at either dose.

Unlike its actions on stomach motility, CFCL administered at 1000 mg/kg, increased the strength of the contractions of the small intestine up to approximately 2000%, but did not affect rate of contractions in any of the animals at this dose. The effects after CFCL administration at 300 mg/kg were variable.

CEZ at doses of 300 and 1,000 mg/kg had a positive effect on both stomach and small intestine contractions. The strength of stomach contractions was increased by up to 267% following the 300 mg/kg dose and 4550% following 1,000 mg/kg dose. CEZ had little effect on rate of contractions. The onset of the increase in contractions occurred within 5 minutes post-dose, although peak increase was not attained, in some cases, until approximately 30 minutes post-dose.

Administration of CEZ (300 and 1000 mg/kg) had a marked effect on small intestine activity. Strength of contraction was increased by up to 1033 % (1000 mg/kg), and rate of contraction by up to 600% (300mg/kg).

3) Effect on gastric secretion (Table 1)

CFCL and CEZ were examined for effects on gastric secretion and damage using the pylorus-ligated (Shay) rat model. The compounds were examined at intravenous doses of 300 and 1000 mg/kg.

Compound CFCL at 1000 mg/kg caused a weak to moderate, but statistically significant

decrease in gastric K^+ and H^+ output. No other noteworthy effects were observed.

Compound CEZ caused a dose-related decrease in volume of gastric fluid, with concomitant observed decreases in gastric ion secretion which were all statistically significant at 1000 mg/kg. The only noteworthy effect on gastric ion concentration however, was a decrease in H^+.

4) Effect on salivary excretion

Intravenous administation of vehicle, CFCL (250, 500 mg/kg) or CEZ (500 mg/kg) did not induce a flow of saliva from the parotid gland in any of the animals at these doses. There was no resting secretion of saliva salivary flow only occurs in response to a secretogogue. Therefore in conclusion, neither CFCL nor CEZ when administered intravenously, act as secretogogues in the anaesthetised rat.

5) Effect on bile and pancreatic secretions (Tables 2 and 3)

Bile secretion was unaffected by administration of either vehicle or CFCL at doses of 250 and 500 mg/kg. Administration of CEZ at 500 mg/kg induced a marked increase in bile output in all of the 9 surviving animals, with a maximum individual increase of 224%.

Pancreatic secretions were subject to considerable inter-group and inter-animal variation. Observation of individual data indicated that administration of both vehicle and CFCL (250, 500 mg/kg) did not modify pancreatic output. The effects following administration of CEZ were variable although there were indications to suggest that CEZ also elicited a reduction in pancreatic output, although evidence for the latter finding is not conclusive.

6) Effects on urine and electrolytes (Tables 4 and 5)

Intravenous administration of CFCL caused no changes in urine volume at a dose of 300 mg/kg but a large and statistically significant increase in urine volume was observed up to 5 hours post-dose following treatment at 1000 mg/kg. No changes in urinary electrolyte excretion or total protein content of the urine were observed following intravenous administration of CFCL at a dose of 300 mg/kg. At a dose of 1000 mg/kg, however, Na^+, K^+ and Cl^- ion excretion were all significantly elevated as was the total protein content of the urine.

No changes in the volume of urine excreted were observed following intravenous treatment with CEZ at doses of 300 or 1,000 mg/kg. A small but statistically significant reduction in K^+ ion excretion was observed .

Significant elevation in Na^+ excretion was noted at a dose of 1,000 mg/kg.

The reference standard frusemide (2 mg/kg) significantly increased urine volume throughout the experiment and Na^+ and Cl- ion excretion were also significantly increased. Protein content and K^+ ion excretion were unaffected.

7) Effect on renal function

Both CFCL and CEZ increased urine flows in the 20 minutes following administration, but the effects in general however, were not notably different from that caused by vehicle administration.

The glomerular filtration rates for inulin and P.A.H. were not consistently affected by the doses of either CFCL or CEZ.

8) Local anaesthetic activity

i) Corneal reflex (Table 6)

Topical administration of CFCL and CEZ at concentrations of 5 and 10% w/v produced no significant effect on corneal reflex in the guinea-pig. Lidocaine at concentrations of 1 and 2% w/v produced a good dose-related local anaesthetic effect, which was statistically significant at the highest concentration of 2% w/v.

ii) Weal test (Table 7)

Intradermal administration of CFCL and CEZ (5 and 10% w/v) had no significant weal anaesthetic activity. Lidocaine caused a marked and statistically significant inhibition of the pinkrick response.

Discussion

In the anaesthetised dog, administration of CFCL increased small intestine motility and reduced the muscle activity of the stomach. The frequency of the contractile responses following both CFCL and CEZ however, was not affected and it is unlikely that the conduction speed of the gastro-intestinal contents would be changed. This observation is supported by the results of the charcoal propulsion in mice test where the transit time of a charcoal

meal was unaffected by either treatment.

Secretory function would seem to be unaffected by intravenous administration of CFCL, gastric, salivery, pancreatic and bile secretion levels being unchanged. In contrast, however, CEZ administration resulted in a slight reduction in overall gastric volume and H^+ concentration following 1000 mg/kg, a marked increase in bile secretion after 500 mg/kg and a possible decrease in pancreatic output.

Effects on the kidney were only observed following the higher doses of CFCL. In rats CFCL 1000 mg/kg caused a significant increase in the urine volume excreted which was paralleled by marked increases in Na^+, K^+ and Cl^- output. Increased Na excretion was also seen following CEZ although a notable increase in urine output was not observed. The small reduction in K excretion may have gone some way to compensate.

Slight increases in urine output were similarly observed in the anaesthetised dog following CFCL and CEZ but whether the change was treatment-related is equivocal since similar changes also occurred after vehicle. The glomerular filtration rate was unaffected by either test compound.

CFCL and CEZ were both without local anaesthetic activity either topically or when administered intradermally.

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Cefclidinの一般薬理作用：消化器系・腎機能への影響

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Cefclidin(CFCL)の一般薬理試験の一環として，消化器系・腎機能などに対する影響について，cefazolin（CEZ）を比較薬剤として検討した。

CFCLは麻酔犬において，300mg/kgでは明確な変化を示さなかったが，1000mg/kgで胃の収縮抑制と小腸の収縮亢進を示した。しかし，収縮頻度には影響しなかった。また，マウスの消化管輸送能は変化しなかった。その他，胃液分泌，膵液・胆汁分泌，唾液分泌には影響しなかった。CEZは消化管収縮を増加し，胃液および膵液分泌の低下，胆汁分泌の増加が認められた。

一方，尿・電解質排泄については，CFCLの300mg/kgではまったく影響しなかったが，1000mg/kgで尿量・電解質排泄ともに増加した。しかし，糸球体ろ過率には有意な変化がなかった。その他，CFCLは局所麻酔作用を示さなかった。

以上，CFCLは消化器系に対する影響は極めて少なく，また尿量の増加に伴う電解質排泄の増加も，高用量で認められた作用であり，特に問題となる変化ではないと考える。

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