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Effects of various cephem antibiotics on ethanol metabolism and their structure-activity relations

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The effects of various cephem antibiotics and related compounds on ethanol metabolism were studied in association with their chemical structures. In rats, cefoperazone, cefbuperazone, cefamandole, latamoxef, cefmetazole, cefotetan, cefmenoxime and cefminox which have the [(1-methyl-1*H*-tetrazol-5-yl) thio] methyl group at position 3 of the cephem ring caused a significant increase in the blood acetaldehyde concentration. In the last three compounds, disulfiram-like activity was less potent than that evaluated in the preceding compounds. Cefazolin and ceftezole having a 1*H*-tetrazol group at position 7 also showed a disulfiram-like activity. A single administration of 1*H*-tetrazol also increased the blood acetaldehyde concentration. Both blood ethanol and acetaldehyde values were increased significantly on administration of these drugs. In beagle dogs, cefoperazone induced a less remarkable but much more sustained increase in the blood acetaldehyde. These results indicate that the 1*H*-tetrazol group, as well as the [(1-methyl-1*H*-tetrazol-5-yl) thio] methyl group, is responsible for inducing a disulfiram-like action and that there is a difference in the potency of the disulfiram-like activity among the drugs having a [(1-methyl-1*H*-tetrazol-5-yl)thio] methyl group at position 3 of the cephem ring in relation to those in which the side chain is substituted at position 7.

It has been reported that some cephem antibiotics, especially the cephems belonging to the third generation, caused a disulfiram-like action in clinical trials (Reeves & Davies 1980; McMahon 1980; Drummer et al 1980; Neu & Prince 1980). Buening et al (1981) and Yanagihara et al (1982) reported that cefamandole, cefoperazone and cefmetazole caused a marked increase of blood acetaldehyde concentration in rats compared with that in control animals after ethanol administration. All these β-lactams have a [(1-methyl-1*H*-tetrazol-5-yl) thio]-methyl (MTTM) group in the side chain at the 3-position of the cephem ring. From these findings, it can be assumed that the MTTM group at the position 3 of $^{3}\Delta$-cephem-4-carboxylic acid plays a role in the production of a disulfiram-like reaction by these antibiotics.

Therefore, we set out to compare the effects of various cephem antibiotics and related compounds on ethanol metabolism, and to find out the chemical structure that induced disulfiram-like activity in the cephem antibiotics.

MATERIALS AND METHODS

Animals. Male Wistar strain rats, 240–260 g, and beagle dogs, 8·0–13·5 kg, were used; 5 animals were used in each group.

Drugs. The drugs used were: cefotaxime sodium (Hoechst), cefuzoname sodium (Lederle), cefazolin sodium (Fujisawa), ceftezole sodium (Chugai), cefatrizine (Bristol), cefmenoxime hydrochloride (Takeda), cefamandole sodium (Lilly), cefoperazone sodium (Toyama), cefotiam dihydrochloride (Takeda), latamoxef sodium (Shionogi), cefmetazole sodium (Sankyo), cefminox sodium (Meiji), cefotetan (Yamanouchi) cefbuperazone sodium (Toyama), 1-methyl-1*H*-tetrazol-5-yl-thiol (MT) 1*H*-tetrazol (TZ) and disulfiram. MT was kindly provided by Lederle, and TZ and disulfiram were purchased from Tokyo Kasei and Wako, respectively. Cephem antibiotics except cefatrizine were administered intravenously twice a day for 3 consecutive days (at 0900 and 1700 h). Cefatrizine was administered orally twice a day for 3 days. Disulfiram was administered orally once a day for 3 days, while both MT and TZ were administered intravenously by a single injection. After drug administration, animals were fasted for 16 h, but had free access to water. Thereafter, ethanol, 2 g kg^{-1}, was given orally to the animals in a volume of 10 ml kg^{-1} in 20% solution. At 1, 2, 4 and 8 h after the ethanol, 0·5 ml of blood was taken into a heparinized syringe from the heart to determine blood ethanol and acetaldehyde levels. The concentrations of ethanol and acetaldehyde were determined according to a modification of the method of Hishida (1976). In short, 0·5 ml of blood was put into a 5 ml vial containing 0·5 ml of 0·04%

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n-propanol, used as an internal standard. The vial was tightly closed with a rubber stopper and aluminum cap and incubated for 15 min at 55 °C. Then, 500 μl of gas occupying the head space was withdrawn by a gas-tight syringe and injected into a gas chromatograph (Shimadzu, Model GC-4CM) with a glass column (3·0 mm × 2·0 m) packed with Chromosorb 101 (80–100 mesh). Chromatographic conditions were as follows: column temperature, 120 °C; injection port temperature, 150 °C; nitrogen gas flow rate, 50 ml min^{-1}. Data processing was done with Chromatopac C-R3A. Under these conditions, the retention times for acetaldehyde, ethanol and n-propanol were 1·9, 2·7 and 6·0 min, respectively.

RESULTS

Table 1 shows the changes in blood ethanol level elicited by various cephem antibiotics in rats. Blood ethanol concentrations were not elevated significantly until 2 h after ethanol administration for all drugs tested. At 4 h, however, the concentration increased significantly after cefazolin, ceftezole, cefmenoxime, cefiminox and cefotetan at a dose of 400 mg kg^{-1}. With cefamandole and cefoperazone significant increases were brought about at doses of 200 mg kg^{-1} or higher. Latamoxef, cefmetazole and cefbuperazone caused a noticeable increment at doses of 100 mg kg^{-1} or larger. After cefoperazone and cefbuperazone (400 mg kg^{-1}), a significant increase was observed 8 h after ethanol administration. Table 2 shows the changes in blood acetaldehyde values elicited by various cephems in rats. Cefotaxime, cefuzoname, cefatrizine and cefotiam caused no increase in blood acetaldehyde level even at 400 mg kg^{-1}. On the contrary, a significant increase of the blood acetaldehyde values were elicited by cefazolin (400 mg kg^{-1}; 2 h), ceftezole (400 mg kg^{-1}; 1–2 h), cefmenoxime (400 mg kg^{-1}; 1–2 h), cefmandole (100 mg kg^{-1}; 1–2 h, 200 mg kg^{-1}; 1–4 h, 400 mg kg^{-1}; 1–8 h), cefoperazone (100 mg kg^{-1}; 1–4 h, 200 and 400 mg kg^{-1}; 1–8 h), latamoxef (100 mg kg^{-1}; 1h, 200 and 400 mg kg^{-1}; 1–8 h), cefmetazole (100 mg kg^{-1}; 1 h, 200 and 400 mg kg^{-1}; 1–8 h), cefminox (400 mg kg^{-1}; 1–8 h), cefotetan (400 mg kg^{-1}; 1–8 h) and cefbuperazone (100 mg kg^{-1}; 4–8 h, 200 and 400 mg kg^{-1}; 1–8 h). When the blood acetaldehyde concentration of samples obtained from saline-injected animals 2 h after alcohol administration was analysed 3 times per sample at 30 min intervals, no change in the values was observed.

In beagle dogs, cefoperazone (400 mg kg^{-1}) also

Table 1. Changes in blood ethanol concentrations elicited by various cephem antibiotics in rats.

Drugs	Dose[1]	Route	Ethanol concentration (mg ml^{-1}) 1	2	4	8 h
Saline	—	i.v.	1·64 ± 0·32	1·36 + 0·29	0·51 ± 0·05	0·06 ± 0·01
Cefotaxime	400	i.v.	1.66 ± 0·09	1·45 ± 0·10	0·82 ± 0·12	0·02 ± 0·01
Cefuzoname	400	i.v.	1·73 ± 0·40	1·38 ± 0·30	0·47 ± 0·03	0·02 ± 0·01
Cefazolin	400	i.v.	1·93 ± 0.47	1·77 ± 0·46	1·19 ± 0·24*	0·03 ± 0·01
Ceftezole	400	i.v.	2·05 ± 0·10	1·89 ± 0·09	1·32 ± 0·08**	0·06 ± 0·02
Cefatrizine	400	p.o.	1·51 ± 0·17	1·24 ± 0·22	0·80 ± 0·21	0·02 ± 0·01
Cefmenoxime	400	i.v.	1·51 ± 0·06	1·33 ± 0·07	0·82 ± 0·11*	0·11 ± 0·08
Cefamandole	100	i.v.	1·11 ± 0·04	0·97 ± 0·02	0·59 ± 0·05	0·04 ± 0·03
	200	i.v.	1·29 ± 0·08	1·19 ± 0·10	0·85 ± 0·08**	0·06 ± 0·04
	400	i.v.	1·78 ± 0·06	1·50 ± 0·10	1·03 ± 0·08**	0·14 ± 0·04
Cefoperazone	100	i.v.	1·22 ± 0·07	0·97 ± 0·06	0·56 ± 0·08	0·02 ± 0·01
	200	i.v.	1·27 ± 0·07	1·10 ± 0·11	0·86 ± 0·03**	0·15 ± 0·05
	400	i.v.	1·41 ± 0·17	1·33 ± 0·18	1·14 ± 0·19**	0·17 ± 0·04*
Cefotiam	400	i.v.	1·53 ± 0·09	1·61 ± 0·18	0·73 ± 0·13	0·05 ± 0·03
Latamoxef	100	i.v.	1·53 ± 0·10	1·32 ± 0·05	0·98 ± 0·06**	0·09 ± 0·05
	200	i.v.	1·40 ± 0·08	1·32 ± 0·03	1·08 ± 0·03**	0·14 ± 0·05
	400	i.v.	1·54 ± 0·03	1·36 ± 0·08	1·08 ± 0·07**	0·15 ± 0·05
Cefmetazole	100	i.v.	1·23 ± 0·06	1·06 ± 0·05	0·85 ± 0·05**	0·23 ± 0·04
	200	i.v.	1·29 ± 0·06	1·22 ± 0·05	0·86 ± 0·08**	0·20 ± 0·09
	400	i.v.	1·12 ± 0·26	1·18 ± 0·20	0·95 ± 0·05**	0·14 ± 0·04
Cefminox	400	i.v.	1·09 ± 0·15	0·98 ± 0·07	0·81 ± 0·11*	0·03 ± 0·02
Cefotetan	400	i.v.	1·08 ± 0·01	1·01 ± 0·10	0·82 ± 0·02**	0·12 ± 0·05
Cefbuperazone	100	i.v.	1·25 ± 0·10	1·07 ± 0·01	0·75 ± 0·04**	0·10 ± 0·06
	200	i.v.	1·39 ± 0·07	1·29 ± 0·03	0·88 ± 0·05**	0·14 ± 0·02
	400	i.v.	1·94 ± 0·11	1·43 ± 0·14	1·01 ± 0·09**	0·13 ± 0·01**

[1] Drugs were administered twice a day for 3 consecutive days (at 0900 and 1700 h).
*,**: Significantly different from the saline-treated group with $P < 0·05$, $P < 0·01$.

Table 2. Changes in blood acetaldehyde concentrations elicited by various cephem antibiotics in rats.

Drugs	Dose[1]	Route	Acetaldehyde concentration (μg ml^{-1}) 1	2	4	8 h
Saline	—	i.v.	0·29 ± 0·09	0·30 ± 0·06	0·27 ± 0·05	0·18 ± 0·03
Cefotaxime	400	i.v.	0·27 ± 0·06	0·20 ± 0·11	0·18 ± 0·02	0·17 ± 0·03
Cefuzoname	400	i.v.	0·24 ± 0·06	0·18 ± 0·03	0·18 ± 0·03	0·19 ± 0·04
Cefazolin	400	i.v.	0·48 ± 0·13	0·82 ± 0·23*	0·39 ± 0·19	0·20 ± 0·17
Ceftezole	400	i.v.	1·10 ± 0·25*	0·89 ± 0·20*	0·45 ± 0·19	0·21 ± 0·14
Cefatrizine	400	p.o.	0·31 ± 0·20	0·18 ± 0·11	0·18 ± 0·11	0·12 ± 0·08
Cefmenoxime	400	i.v.	1·49 ± 0·42*	1·64 ± 0·58*	1·11 ± 0·49	0·40 ± 0·10
Cefamandole	100	i.v.	2·49 ± 0·48**	0·80 ± 0·21*	0·56 ± 0·16	0·12 ± 0·05
	200	i.v.	4·13 ± 0·30**	2·02 ± 0·56**	1·51 ± 0·15**	0·20 ± 0·13
	400	i.v.	5·06 ± 0·52**	4·98 ± 1·07**	6·86 ± 0·85**	1·03 ± 0·10**
Cefoperazone	100	i.v.	1·28 ± 0·23**	1·99 ± 0·30**	1·09 ± 0·25**	0·44 ± 0·12
	200	i.v.	3·98 ± 0·72**	5·51 ± 1·17**	3·59 ± 1·00**	1·92 ± 0·58**
	400	i.v.	9·29 ± 0·38**	8·37 ± 0·55**	8·03 ± 0·72**	2·80 ± 0·50**
Cefotiam	400	i.v.	0·48 ± 0·15	0·39 ± 0·18	0·33 ± 0·07	0·35 ± 0·16
Latamoxef	100	i.v.	1·79 ± 0·52**	1·11 ± 0·67	1·17 ± 0·62	0·50 ± 0·16
	200	i.v.	6·02 ± 1·77**	6·39 ± 1·08**	5·09 ± 0·96**	1·86 ± 0·12**
	400	i.v.	7·95 ± 1·48**	9·74 ± 0·33**	7·31 ± 1·20**	3·21 ± 1·12**
Cefmetazole	100	i.v.	1·94 ± 0·56*	1·54 ± 0·70	0·98 ± 0·52	0·16 ± 0·09
	200	i.v.	3·96 ± 1·03**	4·78 ± 0·89**	4·56 ± 0·86**	0·70 ± 0·19**
	400	i.v.	5·59 ± 1·61**	5·88 ± 0·26**	4·89 ± 0·58**	0·92 ± 0·24**
Cefminox	400	i.v.	0·90 ± 0·12**	1·09 ± 0·20**	1·62 ± 0·66*	1·52 ± 0·26**
Cefotetan	400	i.v.	1·78 ± 0·36**	1·50 ± 0·38*	1·55 ± 0·50*	0·81 ± 0·26*
Cefbuperazone	100	i.v.	0·67 ± 0·18	0·56 ± 0·21	0·71 ± 0·15*	0·43 ± 0·11*
	200	i.v.	1·96 ± 0·36**	3·20 ± 1·08**	1·48 ± 0·48**	0·51 ± 0·14*
	400	i.v.	8·97 ± 1·27**	7·83 ± 2·00**	5·34 ± 2·81**	1·36 ± 0·28**

[1] Drugs were administered twice a day for 3 consecutive days (at 0900 and 1700 h).
*,**: Significantly different from the saline-treated group with $P < 0·05$, $P < 0·01$.

Table 3. Changes in blood ethanol and acetaldehyde concentrations elicited by cefoperazone and cefuzoname in beagle dogs.

Drugs	Dose[1]	Route	Ethanol concentration (mg ml^{-1}) 1	2	4	8 h
Saline	—	i.v.	1·29 ± 0·32	1·02 ± 0·23	0·81 ± 0·17	0·33 ± 0·05
Cefoperazone	400	i.v.	1·11 ± 0·11	1·11 ± 0·10	0·84 ± 0·09	0·69 ± 0·13*
Cefuzoname	400	i.v.	1·02 ± 0·03	0·98 ± 0·04	0·67 ± 0·05	0·42 ± 0·01

Drugs	Dose[1]	Route	Acetaldehyde concentration (μg ml^{-1}) 1	2	4	8 h
Saline	—	i.v.	0·55 ± 0·11	0·44 ± 0·07	0·21 ± 0·02	0·10 ± 0·01
Cefoperazone	400	i.v.	3·85 ± 1·06*	4·33 ± 1·44*	4·63 ± 1·63*	3·19 ± 0·86*
Cefuzoname	400	i.v.	0·49 ± 0·05	0·42 ± 0·04	0·24 ± 0·06	0·12 ± 0·03

[1] Drugs were administered twice a day for 3 consecutive days (at 0900 and 1700 h).
*: Significantly different from the saline-treated group with $P < 0·05$.

caused an increase of both blood ethanol (8 h) and acetaldehyde levels (1–8 h), but cefuzoname (400 mg kg^{-1}) did not increase either (Table 3).

Table 4 shows the changes in blood ethanol and acetaldehyde levels elicited by MT, TZ and disulfiram. At doses of 200 and 400 mg kg^{-1}, MT elicited a significant increase in both ethanol (4–8 h) and acetaldehyde levels (1–8 h). TZ also significantly increased both ethanol (400 mg kg^{-1}; 4 h) and acetaldehyde levels (200 mg kg^{-1}; 2 h, 400 mg kg^{-1}; 1–8 h). At doses of 100–500 mg kg^{-1}, disulfiram caused an increase in the ethanol level; a significant effect was observed at 4 h (100 mg kg^{-1}) and from 4 to 8 h (200 and 500 mg kg^{-1}). After disulfiram treatment, the increase in acetaldehyde was substantial and long lasting. Significant elevation was

noticed from 1 to 4 h after administration of 100 mg kg^{-1} and from 1 to 8 h after administration of 200 and 500 mg kg^{-1} of disulfiram.

DISCUSSION

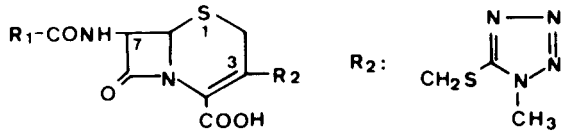
In the present study, it was found that cefazolin, ceftezole, cefmenoxime, cefamandole, cefoperazone, latamoxef, cefmetazole, cefminox, cefotetan and cefbuperazone increased the blood acetaldehyde level after ethanol administration. It has been shown by Buening et al (1981) and Yanagihara et al (1982) that cefamandole, cefoperazone and cefmetazole caused a disulfiram-like action in rats. In the present study, similar findings were observed. It has been postulated that the MTTM side chain is probably the main reason for the disulfiram-like reaction of cephem antibiotics, since not only cefamandole, but also cefoperazone and cefmetazole have the MTTM group at the 3-position of the cephem nucleus. However, in the present experiment, it was found that cefazolin and ceftezole also caused an increase in blood acetaldehyde after ethanol administration. Both these compounds have a TZ group at position 7 of the cephem ring, instead of a MTTM group at the 3-position. From these findings, it is assumed that in some cephem antibiotics, a disulfiram-like reaction may also be elicited by a TZ group in the cephem ring. For this reason, we investigated the influence of TZ alone on ethanol metabolism. As shown in Table 4, a single administration of TZ resulted in a significant increase in blood acetaldehyde at doses of 200 and 400 mg kg^{-1}. This result suggests that the TZ group may also play a role in producing the disulfiram-like reaction of cephem antibiotics regardless of the difference in the position of the substituent group. The disulfiram-like property of MT was more potent than that of TZ. However, cefotiam has a [1-(2-dimethylaminoethyl)1*H*-tetrazol-5-yl-thio] methyl group at position 3 of the cephem ring and showed no disulfiram-like property. Therefore, it may be reasonable to assume that a methyl group at the 1-position of MT may enhance the disulfiram-like property of TZ.

When the blood acetaldehyde concentration per sample was determined repeatedly, there was no apparent change in the values, indicating that loss of acetaldehyde did not take place. In connection with this, Tottmar & Hellström (1983) reported that they did not detect aldehyde dehydrogenase activity in blood from rats. Similar findings were obtained by Deitrich (1966). In his experiments, the process used to obtain the sample involved incubation of the

Table 4. Changes in blood ethanol and acetaldehyde concentrations elicited by disulfiram and tetrazols in rats.

			Ethanol concentration (mg ml^{-1})			
Drugs	Dose[1]	Route	1	2	4	8 h
Saline	—	i.v.	1·64 ± 0·32	1·36 ± 0·29	0·47 ± 0·06	0·04 ± 0·01
1-Methyl-1*H*-tetrazol-5-yl-thiol (MT)	200	i.v.	1·21 ± 0·08	1·12 ± 0·06	0·94 ± 0·06**	0·23 ± 0·04**
	400	i.v.	1·41 ± 0·21	1·91 ± 0·05	1·61 ± 0·16**	0·65 ± 0·16**
1*H*-Tetrazol (TZ)	200	i.v.	1·08 ± 0·12	1·07 ± 0·30	0·51 ± 0·20	0·03 ± 0·01
	400	i.v.	1·13 ± 0·08	1·23 ± 0·19	0·77 ± 0·09*	0·11 ± 0·08
Disulfiram	100	p.o.	1·33 ± 0·08	1·28 ± 0·09	0·80 ± 0·10*	0·04 ± 0·02
	200	p.o.	1·16 ± 0·04	1·17 ± 0·05	0·89 ± 0·03*	0·12 ± 0·03*
	500	p.o.	1·47 ± 0·24	1·46 ± 0·32	1·57 ± 0·13**	0·86 ± 0·16**
			Acetaldehyde concentration (μg ml^{-1})			
Drugs	Dose[1]	Route	1	2	4	8 h
Saline	—	i.v.	0·32 ± 0·10	0·33 ± 0·06	0·25 ± 0·06	0·15 ± 0·04
1-Methyl-1*H*-tetrazol-5-yl-thiol (MT)	200	i.v.	7·31 ± 0·39**	5·61 ± 0·96**	5·85 ± 0·83**	1·55 ± 0·34**
	400	i.v.	10·28 ± 1·93**	13·11 ± 1·55**	9·72 ± 1·44**	5·30 ± 2·22**
1*H*-Tetrazol (TZ)	200	i.v.	1·01 ± 0·39	1·36 ± 0·38**	0·86 ± 0·37	0·47 ± 0·19
	400	i.v.	3·15 ± 0·88**	2·00 ± 0·29**	2·12 ± 0·30**	1·40 ± 0·27**
Disulfiram	100	p.o.	8·36 ± 0·49**	5·88 ± 0·60**	3·35 ± 0·46**	0·74 ± 0·30
	200	p.o.	15·22 ± 1·98**	14·85 ± 1·23**	11·38 ± 1·19**	3·31 ± 0·86**
	400	p.o.	16·63 ± 2·90*	17·27 ± 3·39**	15·24 ± 1·85**	13·71 ± 3·06**

[1] MT and TZ: Single administration (at 1700 h), disulfiram: Once a day for 3 consecutive days (at 1700 h).
*,**: Significantly different from the saline-treated group with $P < 0·05$, $P < 0·01$.



Cephems	R_2:[(1-Methyl-1*H*-tetrazol-5-yl)-thio]methyl	
Drugs	R_1	ED 100 (mg kg^{-1})
Cefoperazone	C_2H_5-N N-C ONHCH- O O OH	130·0 (78·8–214·5)
Cefbuperazone	C_2H_5-N N-CONHCH- O O CH_3CH OH	185·0 (108·8–314·5)
Cefamandole	CH— OH	120·0 (50·0–288·0)
Latamoxef*	HO COOH C— H	125·0 (78·1–200·0)
Cefmetazole	N≡CCH$_2$SCH$_2$–	140·0 (58·3–336·0)
Cefotetan	H_2NOC S HOOC S CH–	>400·0
Cefmenoxime	N C— H_2N S NOCH$_3$	>400.0
Cefminox	NH_3^+ CH–CH$_2$SCH$_2$– COO^-	>400·0

*: Oxacephems.

FIG. 1. Relationship between chemical structure and disulfiram-like property of certain cephem antibiotics. These have a [(1-methyl-1*H*-tetrazol-5-yl)thio] methyl group at position 3 of cephem ring. R_1 is a substituent group at 7-position of cephem ring. ED 100 is the dose required for increasing acetaldehyde level by 10 times the initial value. (ED 100 was estimated after the method of Litchfield & Wilcoxon 1949).

blood at 55 °C for 15 min. Hishida (1976) reported that thermal treatment which does not exceed these conditions in either temperature or duration did not increase acetaldehyde level in the sample artifactually. In Hishida's experiments, as in our own, a consistent value was repeatedly obtained for the same sample.

In the present study, it became clear that there are remarkable differences in the potency of disulfiram-like reactions among the compounds having an MTTM group at position 3 of the cephem ring. Fig. 1 shows the relation between the chemical structure of the substituent group at position 7 and the disulfiram-like reaction of antibiotics having an MTTM group at the 3-position. Cefoperazone, cefbuperazone, cefamandole, cefmetazole and latamoxef possessed a potent disulfiram-like property, while cefotetan, cefmenoxime and cefminox were very weak. Cefoperazone, cefbuperazone, cefamandole and latamoxef have a hydroxy group in the side chain at position 7 of the cephem ring. Cefotetan, cefmenoxime and cefminox have both carboxy group and amino groups, so these are amphoteric, polar compounds. MT itself showed a potent disulfiram-like action even after a single administration; therefore, it can be postulated that amphoteric structure may interfere with the mechanism producing a disulfiram-like reaction. However, the reason why compounds having an amphoteric group showed a weak disulfiram-like property is not clearly understood. Hartesveldt et al (1975) showed that amphoteric compounds such as ampicillin and 6-aminopenicillamic acid had little or no epileptogenic activity, although several penicillin derivatives produced a potent epileptogenic activity. This finding may give some clues towards the elucidation of the reason for a weak disulfiram-like property in amphoteric cephems.

Yamanaka et al (1983) reported that latamoxef and disulfiram caused a significant elevation of blood ethanol compared with the non-treated, control group. On the other hand, Yanagihara et al (1982) reported that cefmetazole, cefamandole and cefoperazone induced an increase of acetaldehyde level without affecting the ethanol level in the same blood samples. They showed that disulfiram caused a significant decrease of ethanol level at 0·5, 1 and 2 h after ethanol administration. The results obtained in the present experiment were in accordance with those reported by Yamanaka et al (1983), that is, all the drugs increasing the blood acetaldehyde level also caused an increase of blood ethanol level. It seems possible that the elevation of the ethanol level in blood may occur as a result of negative feedback driven by acetaldehyde. During treatment with disulfiram, an increase in ethanol concentration in blood was also shown in clinical use (Ritchie 1980).

In the beagle dog experiments, it was also found that cefoperazone caused an increase in blood acetaldehyde, though the extent was weaker than that seen in rats. The result suggests that a disulfiram-like property of cephem antibiotics can be exerted across the species.

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