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Clinical Trial with SQ 11, 302 on Acute Gastroenteritis

by

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Introduction

SQ 11,302, now known as Dexacillin or Epicillin is a new semisynthetic penicillin developed by The Squibb Institute for Medical Research. It is designated chemically as 6-D-2-amino-2-(1,4-cyclohexadien-1-yl) acetamido penicillanic acid.

Pharmacologically, it retains all of the attributes of ampicillin, such as, it is acid resistance and therefore has better absorption, it has minimal toxicity and a wide range of applications. However, it is destroyed by penicillinase and is therefore not effective against penicillinase producing organisms. The drug possesses the same degree of allergic potential as ampicillin. In earlier studies carried out in adult males, SQ 11,302 was absorbed from the gastrointestinal tract, appearing in the blood within one half hour and was rapidly excreted by the kidney. (Squibb, 1970).

Infections caused by the following organisms are expected to respond to therapy with epicillin:

a. Gram positive organisms, i.e. Hemolytic and Nonhemolytic streptococci, Streptococci that do not produce penicillinase, Pneumococci and Corynebacterium species.

b. Gram negative organisms, i.e. Hemophilus influenzae, Neisseria organisms, Proteus mirabilis and many strains of Salmonella, Shigella and Escherichia coli.

Clinically, dexacillin is suggested to be used for therapy in the treatment of certain bacterial infections of the respiratory, genitourinary and gastrointestinal tracts. A clinical trial was carried out with the purpose to investigate the effects and the side-effects of the test drug.

The present paper is a report on the results of epicillin oral suspension in the treatment of acute gastroenteritis in children.

Material and Methods

A group of 50 patients who were hospitalized in The Gastroenteritis Ward, Department of Child Health, Dr. Tjipto Mangunkusumo General Hospital, from August 1970 to January 1971, because of having acute frequent diarrhea with vomiting and dehydration were enrolled in the study.

On the day of admission most of the patients had watery diarrhea frequency from 6 to 20 times a day. The degree of dehydration was usually severe, with waterloss equal to 12% or more of the expected body weight.

Fever was a common finding. The duration of illness before the start of therapy with SQ 11,302 was reported in all patients. It ranged from less than one day to ten days, (average 3 days). Most of the patients were of the lower socio economic class.

Before administration of the drug, a rectal swab specimen for culture was taken from each patient. It was obtained by inserting the rectal swab 2 cm into the rectum and rotated. Then the specimen was sent immediately to The Department of Microbiology for further microbiological examination.

A similar specimen for each patient was taken for culture 24 hours after the start of therapy with epicillin.

The next specimen was taken, planted and tested 24 to 48 hours after stopping therapy.

The following laboratory tests consisting of a complete blood cell count with differential white cells count, blood urea nitrogen (BUN), serum bilirubin, alkaline phosphatase, microscopical stool examination and urinalysis were performed on each patient before starting therapy, at about the midpoint, and after therapy was stopped.

SQ 11,302 was given in the form of oral suspension, the dosage being 50 mg/Kg. body weight/day, divided into four equal doses.

Intravenous fluid drip (IVFD) using 3A solution (containing equal parts of 0,9% NaCl, 5% Glucose, $^1/_6$ Mol. Na-Lactate) and Darrow Glucose solution were given immediately according to the scheme outlined by Sutedjo et al. (1961). Before institution of the drip, alkali reserve was determined in some patients. As soon as rehydration was obtained, the IVFD was stopped and realimentation using diluted milk formula was instituted. As routine KCl/NaCl and vitamins (B complex and C) were given orally during realimentation.

Anti-convulsive drugs such as luminal or largactil were given when convulsions were present, followed by lumbar puncture and cerebrospinal fluid examination.

Therapy was discontinued if the patient improved clinically and microscopical stool examination revealed no abnormalities. Other reasons to discontinue therapy were lack of response and development of adverse reaction.

Results

Among fifty patients, 30 were males (60%) ranging in age between one half to twenty four months (average 7,9 months) and 20 were females ranging in age between two to twenty four months (average 9,6 months).

The clinical symptoms noted on admission were as follows (table 1):

TABLE 1 : *Clinical symptoms on admission in both sexes*

	Number of patients	Percentage %
Frequent diarrhea (of more than 6 times/day)	50	100
Vomiting	50	100
Dehydration (usually severe)	50	100
Fever (38 centigrades or more)	36	72
Cough	21	42
Convulsions	3	6

In all patients frequent diarrhea and vomiting with severe dehydration were the reason for hospitalization.

Table 2 shows concurrent illnesses in both sexes during hospitalization.

TABLE 2 : *Concurrent illnesses during hospitalization*

	Number of patients	Percentage %
Upper respiratory tract infections	21	42
Otitis media	8	16
Malnutrition	4	8
Febrile convulsions	3	6

Laboratory data of liver function tests and BUN obtained preceeding, during and after treatment with SQ 11,302 are shown in table 3.

TABLE 3 : *Laboratory data before, during, after treatment in 50 patients*

Range of normal values *)	Before Treatment		During Treatment		Post-Treatment	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Alkaline phosphatase (10-15 U) **)	43	7	45	5	47	3
Serum bilirubin (0-1 mg%)	50	—	49	1	49	1
B U N (20-40 mg%)	38	12	45	5	47	3

Table 4 shows hematological values for hemoglobin, hematocrit, leukocytes and differential count for eosinophils.

TABLE 4 : *Hemoglobin, hematocrit, leukocytes and eosinophils before, during and after treatment in 50 patients*

Range of normal values *)	Before Treatment		During Treatment		Post-Treatment	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Hemoglobin (10-13.7 gm%)	24	26 (52%)	26	24 (48%)	28	22 (44%)
Hematocrit (30-44 vol%)	45	5 (10%)	47	3 (6%)	49	1 (2%)
Leukocytes (5.100-18.100/mm)	49	1 (2%)	50	—	50	—
Eosinophils	50	—	48	2 (4%)	49	1 (2%)

*) Local laboratory : Normal values for age
**) King-Armstrong units.

Response to therapy of the positive cultures is shown in the following table (table 5)

TABLE 5 : *Before and after treatment of positive cultures*

Micro-organism	Before Treatment Positive Culture		After Treatment Negative Culture		
	Number	Percentage %	0-2 days	3-4 days	4 days
Shigella flexneri	4	8	2	2	—
E. coli	2	4	—	—	1

Twenty five out of fifty patients (50%) passed mucous stools; these findings were in accordance with leukocytes two plusses (++) on microscopical stool examination. However, only 4 rectal swab specimens yielded positive cultures for Shigella flexneri. Two other specimens revealed positive E. coli. Sensitivity testing of positive cultures (Shigella and E. coli) revealed that both organisms were sensitive to SQ 11,302, as indicated by the zone of inhibition around the 10 mcg disc.

Improvement of signs and symptoms after starting therapy is tabulated in table 6.

TABLE 6 : *Signs and symptoms v.s. duration of treatment with SQ 11,302 in 50 patients*

Signs and symptoms	Pre-treatment Number of subjects	Duration of treatment		
		0-2 days Number (%)	3-4 days Number (%)	4 days Number (%)
Diarrhea (frequent, watery)	50	25 (50)	23 (46)	2 (4)
Vomiting	50	38 (76)	12 (24)	— —
Fever	36	10 (20)	18 (36)	8 (16)
Cough	21	3 (6)	10 (20)	8 (16)
Convulsions	3	3 (6)	— —	— —
Leukocytes in the stool (++)	25	5 (10)	16 (32)	4 (8)

Duration of treatment varied from 2-5 days, the average being 3 days, whereas hospitalization lasted from 4 - 11 days with the average of 6 days.

Only in two cases out of the fifty patients adverse reactions were noticed.

One developed skin rash on the second day and the other developed jaundice on the third day of treatment. In no patient relapse was reported and mortality was not found among the group.

Discussion

The overall evaluation of response to therapy with Dexacillin or epicil-

lin in various infectious diseases such as urinary tract, respiratory tract and miscellaneous local infections was reported as excellent by previous studies. The evaluation was based on the clinical response of the patients (improvement in signs and symptoms and the time required for such improvements), the eradication of the organism from the cultures after treatment and whether or not a relapse occurred.

The present study comprises a group of patients with age variations ranging between ½ — 24 months. Diarrhea in this young age group is thought to be a reaction to enteral as well as parenteral stimuli. Etiologic factors of diarrhea in the same age group have been studied previously (Ono Dewanoto et al., 1968; Tumbelaka, 1965; Van Bueren, 1939), and were reported that about 75% were of enteral infection, predominantly caused by E. Coli and Shigellae. The remainder was of parenteral infections or of unknown etiology.

Diarrhea and vomiting are generally improved within the first four days of treatment (Table 6). Dietetic management such as cessation of oral route feeding. followed by intravenous fluid drip and realimentation. with diluted milk formula, accounts for the favourable result obtained.

Diarrhea associated with upper respiratory tract infections is found in 21 patients. Coughing did not respond as rapidly to treatment with epicillin as did diarrhea. Only in 3 cases was coughing alleviated within 2 days, the rest within 4 days or more.

The duration of treatment for diarrhea was relatively shorter as compared with a study using ampicillin and chloramphenicol carried out previously (Sadikin Darmawan et al., 1970). The duration varied from 2 to 5 days, with the average of 3 days.

No clinical failure was noted in the trial.

On admission a fever of 38 centigrades or more was found in 36 patients. It was thought to be due to infection and dehydration as well. In 10 cases the body temperature dropped immediately after administration of IVFD. In 18 patients the body temperature became normal after 4 days of treatment. In the other 8 cases there was complication with otitis and the fever remained fluctuating until a paracentesis was performed.

Three patients had convulsions on admission. Lumbar punctures were performed and cerebrospinal fluid showed no abnormality.

In all cases convulsions subsided on the second day after treatment, followed by normal body temperature. It was thought to be of febrile origin since in all cases convulsions were associated with fever.

Only 4 rectal swab specimens yielded positive culture for Shigella flexneri and two other specimens revealed positive Coli. The low percentage of positive cultures may be caused by the widely use of other antibiotics previous to admission.

Shigella was eradicated from the stool after 3 to 4 days of treatment and E. Coli after 4 to 5 days.

Summary and conclusions

Epicillin designated chemically as 6-D-2amino-2-(1,4 cyclohexadien-1-yl) acetamido penicillanic acid is a new semi-synthetic penicillin. A clinical trial was carried out in 50 patients having acute gastroenteritis, with the dosage of 50 mg/kg body weight.

Evaluation of the results is based on clinical response vs. duration of treatment, eradication of the organism from the culture and whether a relapse occurred. The test-drug is effective. Possible adverse reactions are attributed in only a small number of cases.

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