RESULTS

A- Clinical Part:

This study was carried out on 20 epileptic patients, 12 males and 8 females, with age ranged between (7-70 years), mean age 21.4, as out patients, were randomly allocated to this study.

All patients were on a stable dosage of sodium valproate (30-50 mg/kg . oral / day). The recommended starting regimens were as follows: Sodium valproate (30 mg/kg . oral / day) in two dividing doses, increased by 200 mg/day at weekly intervals until control of seizures, but the total dose after seizures control not exceeds 50 mg/kg/day. oral .

The number of patients with adverse events were 35% (table 3); many reported more than one side effect. The same adverse events reported by the patients at repeat visits were only included once in this analysis. These unwanted effects included sedation in one patient (5%), headache in one patient (5%), tremors in two patients (10%), Rash in one patient (5%), gastrointestinal disturbance in two patients (10%), weight gain in four patient (20%) and appetite gain in two patients (10%) (table 4) .

In the present work, it was found that sedation, headache and tremors developed in patients who needed higher dosage of sodium valproate (Mean 48.3 mg/day) on reduction of dosage, these unwanted effects disappeared (mean dosage 38.6 mg/day). Allergy developed in one patient (5%) in the form of skin rash at the start of the treatment, and

this patient was withdrawn. Moreover, temporary gastrointestinal upset (nausea, heartburn or indigestion) has been detected in 2 patients (10%), in the first month of treatment, but patients were advised to take medication after a meal, and to avoid aerated drinks and they were improved, and continued the treatment.

In addition, our results revealed that, during sodium valproate treatment, an increasing in appetite was recorded in 2 cases and was associated with an increase in body weight, at the end of this trial, one patient showed an increase of about 4 kg and the other was a female and showed an increase of about 5.5 kg, there were two female patients, showed an increase of body weight of about 3.5 kg, and 7 kg without an increase of appetite. Moreover, our results revealed that the 4 patients were on a dosage of 30 mg/kg/oral/day (table 4).

As regard liver function tests there were no significant difference in alkaline phosphates, total protein and albumin levels ($P \geq 0.05$) between control group and after 3 months of treatment, but total bilirubin, SGOT, and SGPT levels were significantly elevated ($P \leq 0.05$) table (5), Fig. (3).

Moreover, there were non significant change in serum prolactin level ($P \geq 0.05$) table (6), fig. (6) .

B- The Experimental part:

It was observed that the mean value of GABA in the different areas of the brain of male normal adult rats was 306 ug/gm ± 2.764 in cerebral cortex, 474 ug/gm ± 2.985 in thalamus, hypothalamus, 423 ug/gm ± 3.711 in midbrain, and 252 ug/gm ± 4.294 in the hindbrain. Administration of sodium valproate 400 mg/kg/day/oral) for 21 days significantly increase GABA level ($P \leq 0.05$) to about 432 ug/gm ± 20.468 (+ 41%) in cerebral cortex, 784 ug/gm ± 74.131 (+56%) in thalamus-hypothalamus, 824 ug/gm ± 68.903 (+95%) in midbrain and 435 ug/gm ± 21.495 (+73%) in hindbrain compared with normal rats table (7), Fig.(7,9).

Regarding 5HT level, its average concentrations were 0.15 ug/gm ± 0.010, 0.29 ug/gm ± 0.011, 0.70 ug/gm ± 0.016, and 0.23 ug/gm ± 0.014 in the cerebral cortex, thalamus, hypothalamus, midbrain and hindbrain respectively in normal non treated rats Table (8), fig. (8,9).

Sodium valproate (400 mg/kg. Oral) for 21 days, there were significant elevation of 5HT levels ($P \leq 0.05$) in cerebral cortex and midbrain, and the levels were 0.22 ug/gm ± 0.003 (+47%) in cerebral cortex, and 1.26 ± 0.016 (+80%) in midbrain, but was significantly reduced ($P \leq 0.05$) in thalamus, hypothalamus to 0.16 ug/gm ± 0.01 (-45%) and was non significantly reduced ($P \geq 0.05$) in hindbrain which was 0.2 ug/gm ± 0.02 (-13%) compared with normal rats table (8) Fig. (8,9).

Finally, sodium valproate administered orally to rats on day 1 to 20 of pregnancy at dose of (400 mg/kg/oral) had non significant effect ($P \geq 0.05$) on the number of resorption and live fetuses table(9), fig.(10). Moreover, maternal body weight was significantly increased ($P \leq 0.05$) but there were non significant increase ($P \geq 0.05$) of fetal body weight compared with control group table (10), fig. (11).

Examination of fetuses of sodium valproate treated maternal rats at day 21 revealed 3 fetuses with short neck (15%) table (11), fig. (13). Moreover, on examination of fetuses skeleton (stained with Alizarin Red dye) there were 6 rats (30%) showed no ossification of lower part of the vertebral column, confirmed by dissection where, there were no cartilaginous elements (spina bifida) table (11), fig. (14 a,b,c). Moreover, there were 3 fetuses (15%) with absence of ossific centers in upper and lower limbs, in addition, there were absence of angle of mandible. Table (11), fig. (15).

Table (3): Total number of patients with adverse drug reactions

Number of patients	20 (12 male, 8 female)
Number of reporting adverse events	7
Percentage with adverse events	35%
Age	Mean age 21.4

Table (4): Number of adverse events reports

Adverse events reported	Number
Neurological	
Sedation	1 (5%)
Fatigue	0
Headache	1 (5%)
Ataxia	0
Tremors	2 (10%)
Dermatological	
Rash	1 (5%)
Alopecia	0
Gastrointestinal	
Nausea, vomiting	2 (10%)
Constipation	0
Diarrhea	0
Endocrinal / Metabolic	
Weight gain	4 (20%)
Appetite gain	2 (10%)
Menstrual disorder	0
Thirst, polyurea	0
Decreased Libido	0
Cardiovascular	
Cardiac failure	0
Dyspnea, syncope	0
Hypotension, Flushing	0
Total	7

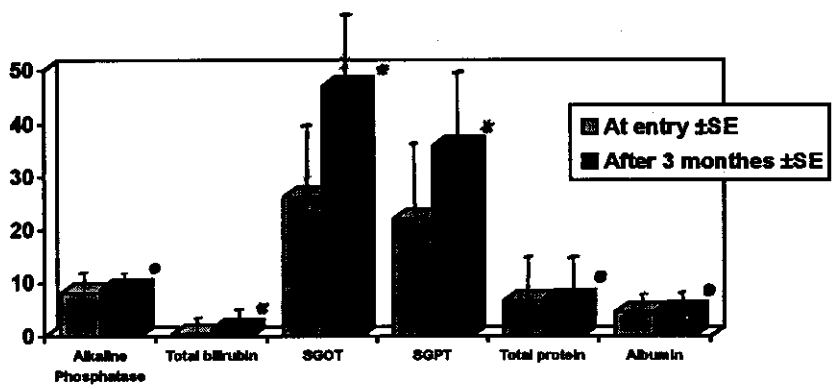

Fig. (3): Liver function test

* Significant at $P \leq 0.05$

• non significant at $P \geq 0.05$

Fig. (4): Light microscopy of liver biopsy of normal non treated rats (H&E x 400)

Fig. (5): Light microscopy of liver biopsy of valproate rats (400 mg/kg/oral/day for 21 days) reveals ballooning degeneration of hepatocytes. (H&E x 400).

Table (6): Serum prolactin level ngm/ml

AT entry ± SE	After 3 months ± SE
9.514 ± 3.597	13.328 ± 1.146•

* Significant at P ≤ 0.05

• non significant at P ≥ 0.05

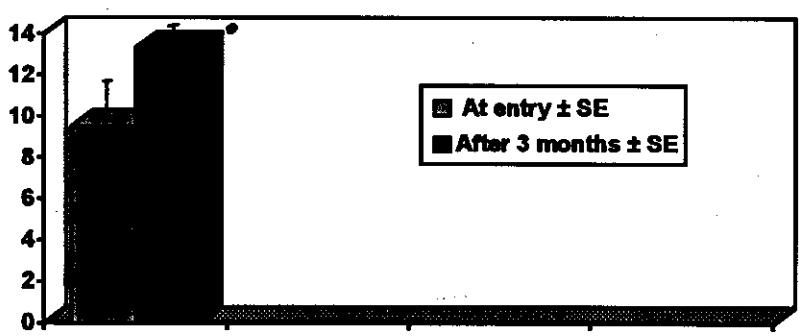

Fig. (6) : Serum prolactin level ngm/ml.

* Significant at P ≤ 0.05

• non significant at P ≥ 0.05

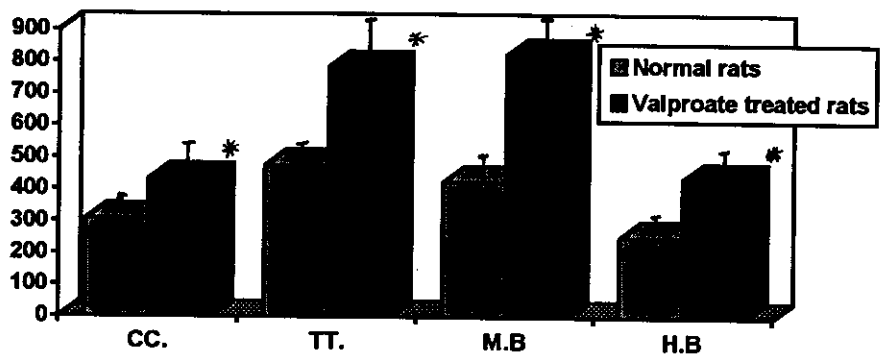

Fig. (7): Effect of sodium Valproate (400 mg/kg/oral/day) for 21 day, on the average concentration (m±SE) of GABA (ug/gm wet tissue) in valproate treated rats compared with normal rats.

* Significant at $P \leq 0.05$

• Non significant at $P \geq 0.05$

C.C. = Cerebral Cortex

T.T. = Thalamus-hypothalamus.

M.B. = Midbrain.

H.B. = Hindbrain.

Table (8): Effect of sodium valproate (400 mg/kg/oral/day) for 21 day, on the average concentration (m±SE) on 5HT (ug/gm wet tissue) in valproate treated rats compared with normal rats

Group / Brain area	Normal rates	Valproate treated rats	% change
C. C.	0.15±0.01	0.22±0.003	+ 47 *
T.T.	0.29±0.011	0.16±0.01	- 45 *
M.B.	0.70±0.016	1.26±0.016	+ 89 *
H.B.	0.23±0.014	0.2±0.02	- 13 •

* Significant at $P \leq 0.05$

• non significant at $P \geq 0.05$

C.C. = Cerebral Cortex

T.T. = Thalamus-hypothalamus.

M.B. = Midbrain.

H.B. = Hindbrain.

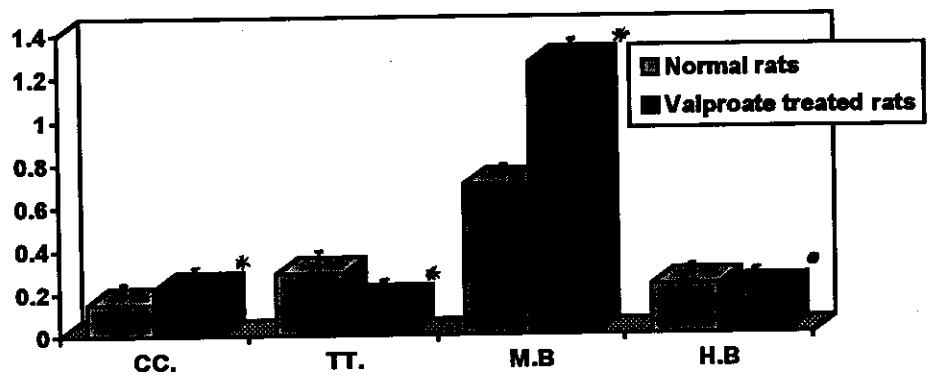

Fig. (8): Effect of sodium valproate (400 mg/kg/oral/day) for 21 day, on the average concentration (m±SE) on 5HT(ug/gm wet tissue) in valproate treated rats compared with normal rats

* Significant at $P \leq 0.05$

• non significant at $P \geq 0.05$

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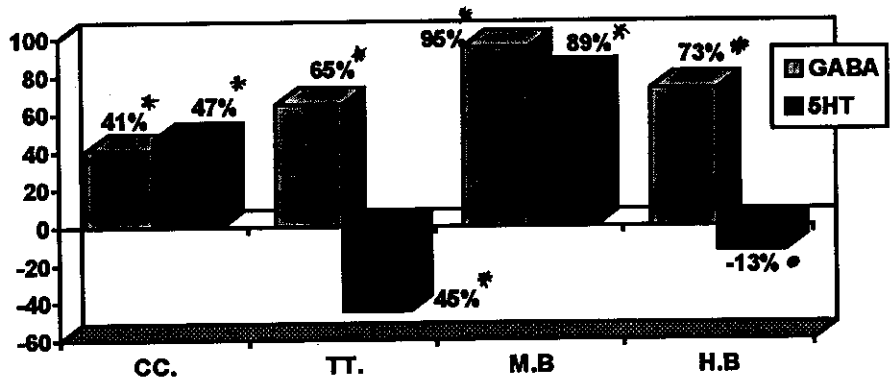

Fig. (9): A bar chart showing % changes in GABA & 5HT concentrations in various areas of rat brain after 21 days of administration of sodium valproate (400 kg/oral/day) compared with normal non-treated rats.

* Significant at $P \leq 0.05$

• non significant at $P \geq 0.05$

C.C. = Cerebral Cortex

T.T. = Thalamus-hypothalamus.

M.B. = Midbrain.

H.B. = Hindbrain.

Table (9): Effect of oral administration of sodium valproate (400 mg/kg/day) to pregnant rats on day 1 to 20 of gestation on the resorption and survival rates (m±SE).

	Normal Rats	Sodium Valproate treated rats
Number of pregnant rats	20	20
Number of Implantation/Litter	9.56±0.36	8.6±0.45•
Number of resorption /Litter	0.31±0.12	0.45±0.21•
Number of Live fetuses/Litter	9.25±0.48	8.15±0.47•

* Significant at $P \leq 0.05$

• non significant at $P \geq 0.05$

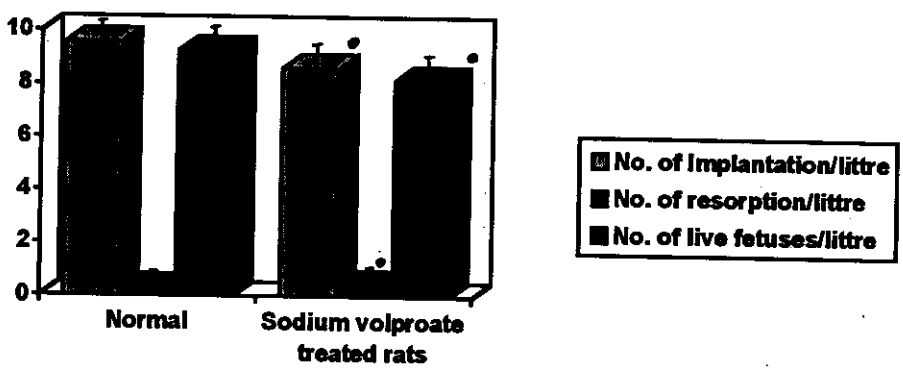

Fig.(10): Effect of oral administration of sodium valproate (400 mg/kg/day) to pregnant rats on the resorption and survival rates (m±SE).

* Significant at $P \leq 0.05$

• non significant at $P \geq 0.05$

Table (10): Effect of oral administration of sodium valproate (400 mg/kg/day) to pregnant rats on maternal body weight gain and fetal body weight (m±SE).

	Normal Rats	Sodium Valproate treated rats
Maternal body weight	36±1.23	51±2.9 *
Fetal body weight	4.5±0.39	3.4±1.2 •

* Significant at $P \leq 0.05$

• non significant at $P \geq 0.05$

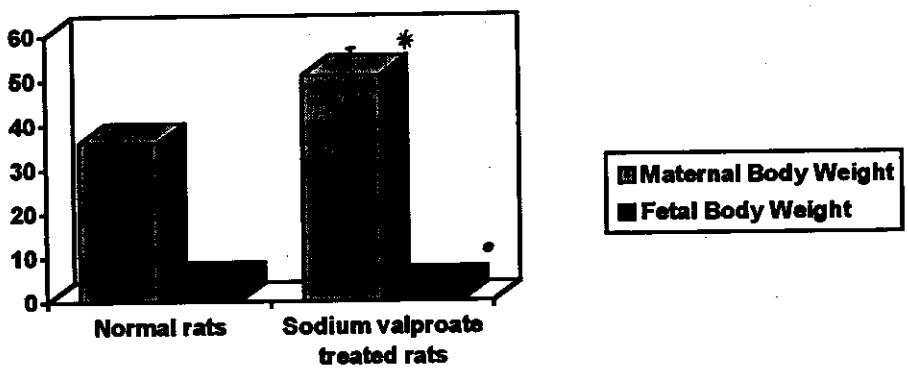

Fig.(11): Effect of oral administration of sodium valproate (400 mg/kg/day) to pregnant rats on day 1 to 20 of gestation on maternal body weight gain and fetal body weight (m±SE).

* Significant at $P \leq 0.05$

• non significant at $P \geq 0.05$

Table (11) Fetuses abnormalities

	Normal fetuses	Fetuses of maternal valproate treated
• Short neck	0	3 (15%)
• Spina bifida	0	6 (30%)
• Absence of angle of mandible, ossific centers in upper, lower limbs	0	3 (15%)

Posterior Lat. view

Fig. (12): A photograph of the skeleton of rat fetus 21 days of gestation

Fig.(13): A photograph of a rat fetus 21 days of gestation after maternal administration of sodium valproate (400 mg/oral/day) showing retarded growth and short neck (lat. View).

Fig. (14): A photograph of a rat fetus skeleton, 21 days of gestation after maternal administration of sodium valproate (400 mg/kg/oral/day), showing spina bifida

Fig. (14, a) : control fetus.

Fig. (14, b) : spina bifida

Fig. (14, c) : Comparison between a control fetus and a fetus of maternal valproate treated rats.

Fig. (14, a)

Fig. (14, b)

Fig. (14, c)

Fig. (15): A photograph of rat fetus 21 days of gestation after maternal administration of sodium valproate (400 mg/kg. oral/ day) showing absence of angle of mandible, ossific centers in upper and lower limbs.

DISCUSSION

A- Clinical Part :

The selection of an anticonvulsant drug depends on the efficacy in control of seizures, on the frequency and the severity of adverse reactions. This study reported the adverse events during treatment with Sodium valproate (*Lewis 1978*). Twenty patients with newly-diagnosed epilepsy were randomly allocated to this study. The recommended starting regimens were as follows: Sodium valproate 30 mg/kg/day.oral, increased by 200 mg/day at weekly intervals until control of seizures but the total dose after seizures control not exceeds 50 mg/kg/day-oral.

In the present study twenty epileptic patients, with mean age of 21.4, treated with sodium valproate and found side effects in 35 % ; these unwanted effects included Sedation (5%), Headache (5%), Tremors (10%), Allergy (5%), Gastrointestinal disturbance (10%), Weight gain (20%) and Appetite gain (10%).

Some unwanted effects may be dose dependent, such as sedation, headache and tremors. Our results were in conformation with the findings reported by many authors (*Raworth and Birchall, 1978, Monnet et al., 1979, Jeavons et al., 1982, Harranz et al., 1982, and Covanis et al., 1983*) they reported that these unwanted effects developed in patients have been on high dosage often exceeding 50 mg/kg daily, and explained disappearance of tremors on reduction of dose to 40 mg/kg. Also,

our results were in accordance with that of *Davidson (1989)* who reported tremors with high serum valproate level (506-1279 μmol/L).

Patients treated with sodium valproate exhibited both toxic reactions and non-dose-related idiosyncratic effects. The latter occurred early in treatment. Rashes occurred in 5% of patients on valproate which is somewhat lower than the range of 10-13% reported by *Covanis et al., (1983)* and in agreement with that of *Dreifuss and Langer (1987).*

Temporary gastrointestinal upset (nausea, indigestion or heart burn), has been detected in 2 patients (10%) taking tablets and occurred within the first month. Patients were advised to take medication after a meal and to avoid aerated drinks. (*Porelton, 1989*)

No alopecia or hair changes were noted during therapy with sodium valproate this was in agreement with the results of *Henriksen and Johanessen (1980)* that hair changes usually dose dependent.

Covanis et al., (1983) reported that hair changes tended to be more common during the latter part of the year, and commonly occurred between 3-6 months after the start of therapy.

During treatment, an increase in appetite was recorded in two cases (10%) and increase in weight in four cases (20%). However, some patients increased in weight without having an increased in appetite, and more commonly in females than in males. These results were in accordance with that of *Davidson (1989) and Covanis et al., (1983).*