

EDITORIAL

## Toxic interactions between lithium and non-steroidal anti-inflammatory drugs<sup>1</sup>

Affective disorder and arthritis are both common conditions, and drugs form the mainstay of treatment for both illnesses. Despite the large variety of agents used to treat both disorders, toxic interactions between psychotropic and the anti-rheumatic drugs seem uncommon. One combination that has recently attracted some attention is lithium toxicity precipitated by certain non-steroidal anti-inflammatory drugs (NSAIDs).

Approximately one million people in the UK suffer from rheumatoid arthritis, and probably a further three million have osteo-arthritis, a substantial proportion of these patients requiring NSAIDs. In the USA in 1982 there were 19 million prescriptions for ibuprofen (Overview, 1986). McCreadie & Morrison (1985) found that 0.77/100 000 of the population were taking lithium which gives a figure of about 40 000 patients taking lithium in the UK. Thus, quite large numbers of people could be taking lithium and NSAIDs together.

This review covers the current literature on lithium NSAID interaction and addresses the question as to possible underlying mechanisms. So far only five cases of lithium toxicity, secondary to the addition of a NSAID, have been reported. Three of these were from the UK, one from France and one from the USA; they occurred over a seven-year period, indicating that these instances are rather rare. There have also been several studies of the effects of NSAIDs on plasma lithium levels and lithium excretion in normal human volunteer subjects. As it is thought that NSAIDs act by inhibiting prostaglandin synthesis, we examine the possibility that prostaglandins may play a role in the excretion of the lithium ion and particularly the role prostaglandins may have in drug-induced lithium nephrotoxicity.

This editorial will cover the following areas.

- (1) The published reports of cases where toxic interactions have been reported.
- (2) Human studies where volunteers stabilized on lithium have been given various NSAIDs, and both lithium levels and lithium clearance have been measured.
- (3) Renal function and other factors which may have affected serum lithium levels.
- (4) Renal function and prostaglandins.
- (5) The possible role of prostaglandins in psychiatric disorder.
- (6) Animal and *in vitro* studies on the effects of lithium, psychotropic drugs, and NSAIDs on prostaglandin synthesis.
- (7) Conclusions.

### CASE HISTORIES

A total of five cases with a raised serum lithium resulting in a clinical episode of lithium toxicity have been reported. These are summarized in Table 1. Three patients with manic depressive psychosis (Imbs *et al.* 1978; Herschberg & Sierles, 1983; Walbridge & Bazire, 1985), one with severe intractable depression (Nadarajah & Stein, 1985), and one with recurrent unipolar depressive illness (Kerry *et al.* 1983) showed such classic signs of lithium toxicity as confusion, unsteadiness, coarse tremor, restlessness, impaired attention, poor concentration and incomprehensible speech when a NSAID was added to their existing treatment regime. In every instance the signs of toxicity were temporary and disappeared after the NSAID was discontinued. Patient No. 2 (Kerry *et al.* 1983) had been physically and mentally well for nine-and-a-half years, maintained only on

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lithium. After a diagnosis of arthritis was made, Piroxicam was introduced, and in the next year she had three admissions with classical signs of lithium toxicity; serum levels were within the toxic range each time. It should be noted that on one occasion she had stopped taking lithium prior to admission. Patient No. 4 (Nadarajah & Stein, 1985) had intractable depression which had failed to respond to ECT, several antidepressants and a subcaudate tractotomy. He was maintained on clomipramine, and the addition of lithium was thought to have given some benefit. After developing arthritis, he was placed on Piroxicam by his general practitioner. He gradually took to his bed, but this was thought to be a consequence of his depression. However, once he stopped eating and drinking he was admitted to hospital and a diagnosis of lithium toxicity was confirmed by his raised serum level of 2.4 mequiv./l (see Table 1). As with the previous patient, although he had stopped

Table 1. Changes in serum lithium concentration in human volunteer subjects after taking lithium and NSAIDs, and case reports of lithium toxicity, following the administration of a NSAID

Author	Subjects			Anti-Rh. drug	Dose of Anti-Rhu. drug (mg)	Lithium dosage (mg)	Baseline serum lithium mequiv./l	Serum lithium after anti-Rh drug mequiv./l
	Age and status	Sex	N					
Imbs <i>et al.</i> (1978)	53 - patient	F	1	Phenylbutazone	750	1000	0.70	1.44
Hirschberg & Sierles, (1983)	56 - patient	M	1	Indomethacin	200	900	0.80-1.40	3.50
Kerry <i>et al.</i> (1983)	56 - patient	F	1	Piroxicam	20	Not stated	0.8-1.40	2.4
Walbridge & Bazire (1985)	65 - patient	F	1	Piroxicam	20	1000	0.5-0.8	1.01-1.18
Nadarajah & Stein (1985)	63 - patient	M	1	Ibuprofen	600	1000	0.5-0.8	0.5-0.8
Frohlich <i>et al.</i> (1979)	Volunteers	—	4	Piroxicam	40	1000	0.6-0.9	2.4
Reimann <i>et al.</i> (1983)	Volunteers	—	10	Indomethacin	150	Variable	0.95	1.5
Reimann <i>et al.</i> (1983)	Volunteers	—	3	Indomethacin	150	Variable	0.68 ± 0.03	0.84 ± 0.06
Reimann & Frolich (1981)	Volunteers	—	5	Diclofenac	150	660	0.63	0.82
Ragheb <i>et al.</i> (1980)	Volunteers	—	3	Ibuprofen	2400	Variable	0.80	1.0 mg
Walbridge & Bazire (1985)	64 - patient	F	1	Ibuprofen	1200	Not stated		
Reimann <i>et al.</i> (1983)	Volunteers	—	10	Aspirin	4000	Variable	0.63 ± 0.03	0.60 ± 0.04
Bendz & Feinberg (1984)	Volunteer	—	1	Aspirin	3900	330	0.41	0.54

  

Author	Subjects			Speed of change	Concomitant disease	Other medication
	Age and status	Sex	N			
Imbs <i>et al.</i> (1987)	53 - patient	F	1	10 days	Cardiac Fracture Phlebitis	Isosobride nitrate Spironolactone Heparin Viloxazine Chlorazepate
Hirschberg & Sierles, (1983)	56 - patient	M	1	9 days	Alcoholism. Liver damage Previous myocardial infarct Arterio-sclerotic heart disease	Aminophylline Zomepirac*
Kerry <i>et al.</i> (1983)	56 - patient	F	1	Not stated	Arthritis	Nil
Walbridge & Bazire (1985)	65 - patient	F	1	Not stated	Osteo-arthritis	Nil
Nadarajah & Stein (1985)	63 - patient	M	1	'Months'	Previous subcaudate tractotomy Osteo-arthritis	Nil
Frohlich <i>et al.</i> (1979)	Volunteers	—	4	5 days	Normal healthy volunteers/ no physical disorders or other drugs	Nil
Reimann <i>et al.</i> (1983)	Volunteers	—	10	7 days		
Reimann <i>et al.</i> (1983)	Volunteers	—	3	6 days		
Reimann & Frolich (1981)	Volunteers	—	5	7 days		
Ragheb <i>et al.</i> (1980)	Volunteers	—	3	7 days		
Walbridge & Bazire (1985)	64 - patient	F	1	7 months		
Reimann <i>et al.</i> (1983)	Volunteers	—	10	7 days		
Bendz & Feinberg (1984)	Volunteer	M	1	7 days		

\*A NSAID which has been withdrawn.

taking lithium, his plasma lithium level remained persistently high for a further three days: only when Piroxicam was stopped did the lithium levels fall to zero, indicating that the Piroxicam had delayed lithium excretion. The final patient (Wallbridge & Bazire, 1985) developed lithium toxicity on two occasions when given concomitant Piroxicam, but never with ibuprofen (see Table 1).

## HUMAN STUDIES

Systematic evaluation of the interaction between lithium and NSAIDs in human volunteers appears to have been prompted by a chance observation made in one patient who had lithium-induced polyuria which responded to indomethacin (Leftwich *et al.* 1977). In metabolic unit studies, volunteers receiving lithium were given a constant sodium intake and lithium levels were checked until they failed to show a daily fluctuation greater than 0.1 mequiv./l before any experimental drug was administered. A placebo was given initially, followed by 7–10 days of an NSAID experimental drug, followed by a further week of placebo. Using this design (Ragheb *et al.* 1980; Reimann & Frolich, 1981; Reimann *et al.* 1983), the effects of indomethacin, ibuprofen, diclofenac, and aspirin, on plasma lithium and renal lithium clearance were studied and the main findings appear to be as follows:

Indomethacin 50 mg tds increased plasma lithium by 50% in three patients, and 30% in four volunteers, reducing renal lithium clearance by 30%. Diclofenac led to a 26% increase in plasma lithium and a 23% decrease in lithium clearance. For ibuprofen, only weak and inconsistent effects were observed. Thus, one patient, who was taking ibuprofen (2.4 g per day), developed nausea and drowsiness during the experimental period, but his plasma lithium level only rose from 0.80 to 1.00. The authors questioned whether his symptoms were due to lithium toxicity or side effects resulting from a rather high dose of ibuprofen. His plasma lithium showed no changes following 1.2 g of ibuprofen. One patient developed lithium toxicity with Piroxicam but not with ibuprofen (Walbridge & Bazire, 1985). Aspirin produced little or no change in plasma lithium levels even at a high dosage of 4 g/day. (Reimann *et al.* 1983). However, Bendz & Feinberg (1984) reported a 43 year-old man who showed a significant rise in plasma lithium, from 0.41 to 0.54 mequiv./l on being given aspirin. Reimann & Frohlich (1984) questioned Bendz's findings, and suggested that they may have been an artefact caused by failure to strictly control sodium intake, as both sodium intake and sodium excretion can profoundly influence lithium excretion. The pattern of lithium-NSAID interaction in human volunteers thus resembles that for the toxic interactions in patients, with indomethacin but not aspirin or ibuprofen, affecting serum lithium levels. Piroxicam has not yet been tested in human volunteers, but as it is a very potent prostaglandin synthesis inhibitor and results in clinical lithium toxicity, it would be of interest to examine its effects in volunteers on lithium levels.

## RENAL MECHANISMS AND OTHER FACTORS WHICH MAY HAVE AFFECTED LITHIUM LEVELS

There are several other factors which independently can affect serum lithium levels and all of these must be considered when assessing a possible newly proposed mechanism of lithium toxicity. These include renal function, the state of hydration, properties of the preparation, gastric function, external temperature and other factors.

Impaired renal function is a major factor in the development of lithium toxicity. Thus in the largest published series of cases of lithium toxicity, 23 patients were reported (Hansen & Amdisen, 1978), and of these 17 had renal insufficiency during the episode of lithium toxicity, with five patients failing to regain normal renal function on recovery. Renal biopsies revealed abnormalities in seven of these patients, suggesting the presence of a chronic nephropathy possibly induced by lithium. In three of the patients hypertonic dehydration was also thought to be a factor. The mechanism whereby renal damage predisposes to lithium toxicity is uncertain, and it may be that a combination of states of sodium depletion or water loss together with renal damage are required

before toxicity develops. A further complicating factor is that some NSAIDs can cause structural damage. Thus, fenclofenac (Raftery *et al.* 1985) and fenoprofen (Kimberley *et al.* 1978; Wendland *et al.* 1980) can cause structural renal damage as well as a reduction in renal function. Piroxicam (Fraiss *et al.* 1983) and indomethacin (Brezin *et al.* 1979; Tan *et al.* 1979; Galler *et al.* 1981) may also produce renal insufficiency. Lithium produces a mild degree of tubular damage (Hansen *et al.* 1979), which may result in marked distal dysfunction and an impaired glomerular filtration rate (Walker *et al.* 1982). Lithium itself is reported to inhibit its own excretion. Renal lithium clearance is normally about 15–20 ml/minute and this may be markedly reduced during an episode of lithium intoxication, with values of 5 ml/minute or less being documented (Haghfelt *et al.* 1971). This inhibiting effect of lithium on its own excretion may explain why toxicity develops so rapidly once the lithium level has risen beyond a critical point.

Two of the five cases in which lithium toxicity was reported also had severe medical illnesses where some degree of renal impairment might have been present prior to the administration of the NSAID. Thus, Shelley (1986) observed not only that renal function is most likely to be adversely affected by a NSAID if impairment is already present, but also that prostaglandins tend to become more active with deteriorating renal failure.

The other three cases of toxicity occurred with one particular NSAID, namely Piroxicam. This drug was developed with the specific aim of having a long half-life (36–48 hours) so that a single daily dose would give 24 hour pain relief and therefore cover the night (Wiseman & Boyle, 1980; Vrhovac, 1984). Indomethacin and aspirin have much shorter half-lives and do not provide such a constant high degree of prostaglandin synthesis inhibition and pain relief. Even if these drugs are taken three times daily, there is low degree of prostaglandin inhibition at night. Possibly this could be why a long acting NSAID such as Piroxicam is rather more liable to result in lithium toxicity.

An alternative explanation for the development of lithium toxicity in these cases may be that they were simply dehydrated as a consequence of their not eating or drinking secondary to their depression, or because of some other incidental illness such as influenza. If this was the explanation, lithium levels would be expected to move in tandem with the degree of dehydration, as might be measured by the haematocrit. More information on the state of hydration is available in two of the five cases. In the case of Hirschberg & Sierles (1983) the patient had a haematocrit of 33.4%, while his plasma lithium level was in the range of 0.8–1.4 mequiv./l. During his episode of lithium toxicity the plasma lithium rose to 3.5 mequiv./l but the haematocrit only rose to 35.6% and so simple dehydration cannot account for the dramatic rise in plasma lithium. In the case of Nadarajah & Stein, the patient's packed cell volume was 44% on admission, and haemoglobin was 14.9 g/100 ml when the lithium level was 2.4 mequiv./l; however, one year later, while off lithium completely, his haemoglobin was 12.8 and the packed cell volume was 37%, suggesting that some dehydration was present when he was admitted, but that it was insufficient to account for his abnormally high serum lithium level.

A host of other factors may also affect serum lithium levels and they should all be briefly considered when trying to assess a possible new causal mechanism for lithium toxicity.

First, there is inter-laboratory variability of measurement (Fry & Marks, 1971) and split samples tested in different laboratories can vary by as much as 0.4 to 1.6 mequiv./l, even when a steady state has been reached (Weir, 1973). The preparation of lithium and its bio availability may also affect serum level. Thus, lithium carbonate can be taken as Camcolit or Priadel, the latter being a slow release form, which is said to produce steadier serum levels with less peaking. However, in several studies variable absorption with slow release preparations of lithium carbonate has been reported (Coppen *et al.* 1969; Caldwell *et al.* 1971; Tyrer *et al.* 1976), while in one meticulous study two sustained release preparations showed slow release *in vitro*, but not *in vivo* (Tyrer *et al.* 1976). Hot weather can cause excess sodium loss in sweat as well as decreased sodium intake due to anorexia and this too can result in increased serum lithium levels (Amdisen, 1980). Gastric emptying, and irregular food intake can also affect serum lithium (Crammer *et al.* 1974). The time interval between ingestion of the lithium and blood sampling may also make a crucial difference in

the serum lithium level. Finally, non-compliance on the part of the patient may also be a factor in some individuals (Blackwell, 1976).

### RENAL FUNCTION AND PROSTAGLANDINS

Lithium excretion is intimately linked to sodium excretion which in turn is regulated by renal prostaglandins (Stokes & Kokko, 1977; Reimann *et al.* 1983). Thus NSAIDs, which act by inhibiting prostaglandin synthesis and reduce sodium excretion (Vrhovac, 1984), might be expected to have some influence on lithium excretion.

In human volunteers, indomethacin reduces glomerular filtration rate, plasma renin activity and, as a consequence, both sodium and water excretion are reduced (Donker *et al.* 1976). These effects are greater among sodium depleted subjects. Among volunteers taking lithium, indomethacin and diclofenac cause a 50% reduction in prostaglandin E2 (PGE2) (Frolich *et al.* 1979; Reimann & Frolich, 1981). However, as aspirin also causes a 70% reduction in PGE2 but does not lead to a decrease in lithium ion excretion (Reimann *et al.* 1983), PGE2, cannot be the prime prostaglandin mediator. Prostaglandin E1 (PGE1) has not yet been measured among subjects taking lithium who also take NSAIDs, but it may be of greater interest because it is a potent inhibitor of vasopressin. In lithium treated rats, Mtabaji *et al.* (1977) showed that water diuresis was insensitive to the effects of vasopressin infusions. However, this sensitivity was restored if Prostaglandin A2 (PGA2) was added to the vasopressin infusion. In the very low doses of PGA2 used there was no independent effect of PGA2 on diuresis.

Lithium can also inhibit the formation of cyclic AMP (Wang *et al.* 1974) in platelets. These investigators measured the effect of lithium on the ability of PGE1 with regard to stimulating the enzyme adenylcyclase. This can be measured by monitoring the production of cyclic AMP from labelled ATP in platelets. PGE1 produces a large (32-fold) increase in cyclic AMP production, but the addition of a high concentration, i.e. 6 mmol of lithium to the platelets inhibits this increase by 29%. This effect is dose dependent, because when only one mmol of lithium was added the reduction in PGE1 induced cyclic AMP production was only 14%. Lithium alone without PGE1 does not alter the basal synthesis of cyclic AMP. Cyclic AMP production was the same when concentrations of 1 mmol and 6 mmol of lithium were added to the incubation fluid. There was a greater degree of inhibition when the platelets with PGE1 were in contact with lithium for one hour, compared with being in contact for only two minutes.

### PSYCHIATRIC DISORDERS AND PROSTAGLANDINS

A number of research workers have attempted to link prostaglandins directly with either schizophrenia or affective disorder, but so far convincing evidence of any causal link is lacking. Feldberg (1976) initially proposed that schizophrenia might be related to an increase in prostaglandin synthesis in certain areas of the brain. He likened the condition of catalepsy in the cat, to catatonia in schizophrenic patients and demonstrated that catelepsy could be induced by intra-cerebral injections of PGE1. Mtabaji *et al.* (1977), on somewhat scanty evidence, proposed that alcoholism might also be related to altered prostaglandin production. Withdrawal of alcohol results in a reduction of PGE1 synthesis, while Rotrosen *et al.* (1980) have demonstrated that PGE1 reverses certain features of the alcohol withdrawal syndrome in alcohol dependent mice, particularly tremor, irritability and the frequency of convulsions.

Abdulla & Hammadah (1975) studied the basal synthesis rate of PGE1 from its precursor in platelets. The rate of manufacture was the same in patients with affective disorder, schizophrenia and normal controls. However, high concentrations of ADP enhanced PGE1 synthesis in the platelets of the depressives and controls by 400–500%, but this enhancement was not present in schizophrenics. In a study of 39 schizophrenics, who satisfied the Research Diagnostic Criteria, and matched controls, Rotrosen *et al.* (1980) found that the platelets from the control subjects had the highest values for PGE1 induced, cyclic AMP accumulation, while medicated schizophrenics had

lower rates, and neuroleptic free schizophrenics had the lowest accumulation rates. Kafka & Van Kammen (1979) also found a reduction in PGE1 induced cyclic AMP production in schizophrenics, but this could only be demonstrated for males and not for females. Recently, Kanof *et al.* (1986) also examined the effect of PGE1 on cyclic AMP accumulation rates, and they confirmed the diminished platelet cyclic AMP response in both schizophrenics and depressives, but this effect was confined to the platelets and could not be demonstrated in leucocytes.

Prostaglandin F2 (PGF2) levels in a small sample of patients with affective disorder have been studied (Gross *et al.* 1977). They showed that lithium resulted in a small but significant elevation in plasma PGF levels. This increase was only apparent after one year and could not be detected in subjects who had only taken lithium for 12 weeks. The effect that psychotropic drugs have on the PGE1 enhancement of adenylyl cyclase and cyclic AMP production has attracted considerable interest because norepinephrine is a potent inhibitor of this enhancement (Murphy *et al.* 1973). Rotrosen (1980) showed that chloral hydrate and alcohol both increase this effect, but that most psychotropic drugs have little or no influence; they tested dopamine, propranolol, chlorpromazine, fluphenazine, haloperidol, promazine, thioridazine, imipramine, amitriptylene, benzotropine, clozapine and morphine. Evidence that prostaglandins are involved in the functional psychoses is presently therefore somewhat scant, but we suggest here there may be a rather more compelling argument for implicating prostaglandins in NSAID induced lithium nephrotoxicity.

### NSAIDS, PSYCHOTROPIC DRUGS, THE KIDNEY AND PROSTAGLANDINS

Certain drugs, but not others, seem to result in lithium induced nephrotoxicity, which in some cases may present clinically as lithium toxicity. Among the NSAIDs there seems to be good evidence that Piroxicam (Kerry *et al.* 1983; Walbridge & Bazire, 1985; Nadarajah & Stein, 1985) can do this. There are case reports that indomethacin (Hirschberg & Sierles, 1983; Frolich *et al.* 1979; Reimann *et al.* 1983) and phenylbutazone (Imbs *et al.* 1978), but not ibuprofen (Walbridge & Bazire, 1985) or aspirin (Benz, 1983; Reimann *et al.* 1983), have been implicated. Piroxicam and indomethacin are highly potent inhibitors of prostaglandin synthesis, whereas ibuprofen and aspirin have roughly the same, and lower, potency in inhibiting prostaglandin synthesis (Flower *et al.* 1985). The mode of prostaglandin inhibition by indomethacin and aspirin is completely different, probably involving a different site on the enzyme cyclo-oxygenase (Flower *et al.* 1985). Considering the psychotropic drugs, there is a single case report of nephrotic syndrome arising from a combination of haloperidol and lithium (Moskovitz *et al.* 1981). In a more systematic study (Lassen *et al.* 1986) prochlorperazine, flupenthixol and haloperidol in combination with lithium caused a mild degree of polyuria, although clinical nephrotoxicity and lithium toxicity were not found to be documented with these combinations. On the other hand, in the same study tricyclic antidepressants in combination with lithium did not cause polyuria and had no effect on renal function. The action of chlorpromazine is more complex. *In vitro*, chlorpromazine is a potent inhibitor of prostaglandin synthesis, but *in vivo* chlorpromazine stimulates prolactin production and prolactin itself stimulates prostaglandin synthesis. Chlorpromazine tends to increase lithium clearance; Sletten *et al.* (1966) showed that a single oral dose of lithium was excreted more rapidly during chlorpromazine treatment.

The question therefore arises: are the psychotropic drugs which can also trigger lithium nephrotoxicity also the more potent prostaglandin synthetase inhibitors, as seems to be the pattern with the NSAIDs? To clarify this issue it would be most helpful to know exactly what various psychotropic drugs do to human renal prostaglandin synthetase activity, but such an investigation has not yet been undertaken. So far, the effect psychotropic drugs have on prostaglandin synthesis has only been studied in three animal preparations, namely rat brain (Schaeffer *et al.* 1978), bovine seminal vesicles (Krupp & Wesp, 1975), and guinea-pig lung (Lee, 1974). The pattern of drug induced prostaglandin inhibition was quite different in these preparations, but this is consistent with the known marked variation in prostaglandin synthetase activity, both between different organs and between different species.

The profile of drugs which inhibit PG synthetase in the rat brain preparation (Schaeffer *et al.*

1978) shows a remarkable similarity to the profile of drugs which can result in lithium-drug induced nephrotoxicity. In this preparation indomethacin produced 80% prostaglandin inhibition, promethazine 67%, chlorpromazine 46%, while aspirin produced only 32%, desipramine 35%, tranlycypromine 19%, various monoamine oxidase inhibitors (MAOIs) such as pargyline and nialmid less than 10%, and Ritalin 10%. Drugs which had scores of greater than 40% inhibition in this preparation have been reported to give either lithium toxicity, or to result in a detectable alteration in renal function in lithium treated subjects. However, drugs with only a mild degree of PG inhibition scoring less than 40% in this preparation, such as aspirin, MAOIs, tricyclic antidepressants, and ritalin have never been associated with lithium induced nephrotoxicity or alterations in renal function.

The pattern of PG synthetase inhibition that psychotropic drugs produced in the other two preparations was, however, rather different. In the bovine seminal vesicle, chlorpromazine, desipramine and anafanil were all fairly potent PG inhibitors, whereas haloperidol was not. Because the lithium haloperidol combination is known to cause CNS toxicity (Cohen & Cohen, 1974), it seems unlikely that CNS toxicity has a prostaglandin mediated mechanism. In the guinea-pig lung preparation (Lee, 1974) MAOIs such as phenelzine and tranlycypromine were very potent PG inhibitors, even more potent than indomethacin; whereas aspirin and chlorpromazine were very weak prostaglandin synthesis inhibitors, while the tricyclics, doxepin and desipramine provided an intermediate level of prostaglandin inhibition.

## CONCLUSIONS

Toxic clinical interactions between lithium and NSAIDs are rare, and probably only occur in a small minority of instances when the two drugs are used together. They seem to occur in only two situations, first in association with the more potent NSAIDs such as Piroxicam, indomethacin and phenylbutazone, which are also very potent PG synthetase inhibitors and, secondly, among medically ill patients who may already have malfunctioning kidneys and who are often subjected to polypharmacy. Although rare, the interaction is of great theoretical interest since it suggests the possibility that when lithium nephrotoxicity occurs as a consequence of the administration of another drug, prostaglandin mechanisms may be involved. Evidence for this derives from the observations that only those NSAIDs which are highly potent prostaglandin synthesis inhibitors seem to result in this interaction, and that psychotropic drugs which interact with lithium in the kidney to produce polyuria also tend to be those drugs which are rather more powerful prostaglandin inhibitors. It is more likely that this effect is mediated by inhibiting the enzyme prostaglandin synthetase, since the profile of NSAID and psychotropic drugs that result in lithium toxicity seems to fit best the profile of prostaglandin synthetase inhibition in at least one animal preparation, namely, the rat brain. Furthermore, in one of the reported cases (Hirschberg & Sierles, 1983) the patient was already taking a NSAID, namely Zomepirac, when the addition of a second NSAID indomethacin triggered off an episode of lithium toxicity. The effects which PGE<sub>1</sub> has on adenylyl cyclase activity and on cyclic AMP production, and which have attracted much interest in psychiatric disorders, may be rather less important as the mediating mechanism, because most psychotropic drugs appear to have little influence on this reaction (Rotrosen *et al.* 1980).

New NSAIDs are being introduced into clinical practice at a rapid rate, and it would be very useful to have advanced knowledge of which drugs can produce this rare but potentially dangerous interaction. Imbs *et al.* (1979) have demonstrated in lithium treated mice that phenylbutazone, but not aspirin, resulted in an increased plasma lithium, a pattern resembling that found in humans. Possibly new NSAIDs should be screened using such animal models. Toxic clinical interactions are uncommon, but appear to be most significant for Piroxicam and indomethacin. These NSAIDs can still be used in conjunction with lithium, but it may be necessary to reduce lithium dosage and monitor plasma lithium levels a little more closely. Other NSAIDs seem to produce only relatively small increments in serum lithium, and unless the patients are also medically ill or on polypharmacotherapy little modification to routine serum lithium monitoring seems to be warranted.

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