LITHIUM: OLD & NEW USES IN MEDICINE

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Lithium has been used in psychiatry since 1949[1]: since the mid 1960s its use has escalated until it is estimated that about 500,000 patients receive it world-wide. Despite many scares lithium is a very safe drug in experienced hands and it has particular importance in the prophylactic treatment of the recurrent affective disorders, the manic-depressive psychoses, where its ability to reduce or abolish the mood swings has undoubtedly improved immensely the quality of life of many patients and their families and saved many lives of those who would otherwise have been led to suicide [2,3].

These psychiatric benefits have been gained from a drug which is a simple metal ion whose chemistry is apparently simple and whose mode of action is unknown. Whatever can be said of lithium, it is of fundamental interest for us to discover what exactly lithium does at the molecular level which makes it so effective in psychiatry since this may give us insight into the most basic features of the cellular response to drugs: lithium does not, after all, have a large and convoluted structure which can make multiple contacts with receptors which may lead to modification of receptor activation. Whatever lithium does, it achieves because it is a highly charged cation with a large hydrated radius and chemical properties which are similar to magnesium [4,5].

During the last decade a new phase of interest in lithium has begun with the discovery of effects which are unrelated to its psychiatric use. Many of these effects are derived from the well established modification by lithium of haematopoeitic processes notably the stimulation by lithium of leucocytosis [6]. Initially this effect was exploited for the treatment of drug-induced haematopoeitic suppression[7,8], for example in chemotherapy of cancers [9,10]. The metal also has effects on immunologic responses to a number of challenges [11]. However, in the process of such investigations it has become clear that lithium can influence a series of cytokines which regulate such cell differentiation not only in blood forming cells but also in other cell types.

Lithium ion selective electrodes are now commercially available and represent the most effective way of ensuring compliance in lithium treated patients [12]. Not only are they accurate within the clinically useful range but they also provide the long-sought opportunity for psychiatrists to measure blood lithium in the presence of the patient who can thereby be challenged about non-compliance or counselled and the dose regulated accordingly. It is possible to reduce the time required to institute lithium therapy because there is no delay in receiving the results of preliminary test doses.

A modified ion-selective electrode technique is under clinical testing for the measurement of cardiac output in patients with cardiovascular disease [13]. A disposable lithium electrode is placed in the arterial line, usually already in place in these patients and a small injection of a lithium salt is made into the venous line, the resultant lithium signal being integrated on a microcomputer connected to the electrode. Such a process can replace techniques currently in use and which require the insertion of additional cannulae into an already seriously ill patient.

An effect of lithium on virus replication was demonstrated in the early 1980s and this has formed the basis for the topical treatment of Herpes simplex by lithium succinate ointment [14]. Other dermatological responses soon were seen and in Britain, lithium is licenced for the treatment of seborrhoeic dermatitis [15]. A detailed

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study of the effects of lithium on essential fatty acid metabolism showed that it interfered with the fungi of the Pityrosporum sp. which are the ultimate cause of the latter disease. In the course of related studies it was found that the lithium salt of the essential fatty acid, gamma-linoleic-acid (LiGLA) was cytotoxic to a wide range of cancer cells in cultures, apparently because of its inhibition of the 6-desaturase enzyme which is the rate limiting step on the metabolic pathway of both the (n-3) and (n-6) unsaturated fatty acids [16,17]. Clinical trials are currently under way and results are encouraging. Because of the effects on cytokine production, lithium ion alone has been shown to have direct effects on cancer cell proliferation.

Perhaps the most significant new area of influence derives from the inhibition of viral replication. It has been shown that lithium reverses the development of the disease process in murine immunodeficiency disease, the so called mouse AIDS (MAIDS) virus [7,18]. This was discovered because lithium was tested as a means of stimulating leucocyte production in AIDS patients treated with Zidovudine (AZT) whose haematopoeiesis was compromised by the administered drug. Lithium not only reversed the leucopaenia, but also, in the control groups of MAIDS infected animals, lithium had a direct effect on the viral replication and reversed the lymphoma commonly seen in these animals. After lithium, the virus content of tissues markedly declined and the lymphoma apparently disappeared. Human AIDS infected cell lines also appear to be affected in a similar way[18] and clinical trials in human AIDS patients are now under way.

That all this can be achieved by a metal ion salt which can be dug out of the ground in North Carolina is, of course, not popular with the 'Ethical' drug companies and there is little funding of such research. It is clear that lithium has a future in therapeutics but that in order to develop to its full potential it will be necessary to overcome both long-standing prejudice resulting from early therapeutic mistakes, now rare or entirely absent, and the interests of the pharmaceutical industry. Lithium salts are safe. They are safer in general use than the tricyclic antidepressants: they are only extremely rarely associated with suicides and their safety record has been scrutinised as has that of few other drugs over nearly half a century of use. The standardised mortality of lithium patients reported in a meta-analysis of some 15,000 patients was about 1 per 100,000 compared with a figure of about 9 per 100,000 for a non-lithium treated population with affective disorders [19]. Lithium is not commonly associated with suicide and it appears to reduce the excess mortality from all causes seen in affective disorder patients.

Lithium also has significance in basic physiological science. It is used as an inhibitor of the inositol monophosphate phosphatase point of convergence of the triphosphoinositol signalling pathway and whose inhibition results in depletion of the inositol pool on which such signalling depends [20]. The proposal that this inhibition is the locus of action of lithium in the recurrent affective disorders is disputed on the grounds that insufficient lithium is present intracellularly as determined by lithium Nuclear MagneticResonance Spectroscopy (Li-NMR) and indeed this evidence calls into question the whole concept of cellular metal-ion regulation as it is presently understood [4,5].

Lithium is a fascinating metal. It is the smallest and lightest solid element and yet it has such a wide diversity of effects. We believe that its apparent simplicity is a key to its mode of action: whatever it does, it is at a very fundamental level of organisation. If we can gain some clues to lithium's site of action we may well be able to unravel other problems in the field of drug-receptor interactions. Both clinical and experimental approaches are required and these may lead to yet more diverse uses for this element.

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