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ORIGINAL PAPER

Emergence of antidepressant induced suicidality

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In the course of a randomised double-blind crossover study comparing the effects of reboxetine and sertraline in a group of healthy volunteers, two volunteers became suicidal on sertraline. This paper describes the characteristics of the reactions experienced by both subjects. These problems were associated with a combination of akathisia and disinhibition. Dysphoric or akathisic responses on their own to either drug did not lead to suicidality in this group of subjects. Primary Care Psychiatry 2000; 6:23–28, Copyright © 2000 by LibraPharm Limited

Introduction

In 1990, Teicher and colleagues reported on the emergence of suicidality on fluoxetine in a group of six patients {1}. These reports were followed-up by reports from King *et al.* {2}, Creaney *et al.* {3}, Rothschild and Locke {4} and Wirshing *et al.* {5}, among others, reporting other cases where suicidality appeared to emerge in individuals taking fluoxetine.

There were a number of factors associated with these case reports that argued for a strong causal connection. In general there was consistency across the reports as to the time of onset of the problems following intake of fluoxetine. There appeared to be a dose response relationship with problems liable to emerge on a higher dose. There was some agreement as regards the probable mechanism leading to the difficulties. This was termed akathisia, although whether it was quite the same phenomenon as akathisia traditionally associated with neuroleptics was less clear. The phenomenon in general cleared up on discontinuation of treatment and re-emerged in a number of cases on re-exposure to the original treatment. In cases where it re-emerged there were reports that agents, which theoretically might block the appearance of a 5HT mediated problem, were able to minimise or block the emergence of suicidality on re-exposure.

Nevertheless, despite a number of indicators for very clear causal linkage between the intake of fluoxetine and suicidality, there were also a number of aspects of the reports, which argued for some caution in the interpretation of what was happening. One was that some but not all of the patients were on other medication. Another was that some but not all had lengthy psychiatric histories with evidence of personality problems. It was, in general, less than clear what the description of this problem emerging in tertiary care centres might mean for the wider world of primary care antidepressant prescribing.

Following the release of fluoxetine a number of other SSRIs appeared on the market including sertraline and paroxetine. It seems clear that in general these drugs are associated with common profiles of both main effects and side effects. All have received licenses for a similar set of nervous conditions. All produced a set of side effects including extra-pyramidal side effects, which are not generally seen with other antidepressants {6}. Both sertraline and paroxetine have been associated with reports of akathisia {6,7,8,9,10,11,12,13}.

On this basis there would seem therefore to be a possibility that other SSRIs might similarly induce suicidality. A meta-analysis of trials involving the SNRI milnacipran compared with SSRIs showed a significantly increased rate of suicidality on treatment with SSRIs {14}. A randomised placebo control trial of paroxetine in recurrent major depression showed a higher rate of suicide attempts on paroxetine than on placebo in this group of patients

{15}. These data supplement unpublished RCT data from Lilly suggesting a significantly higher rate of suicide attempts in patients taking fluoxetine compared with placebo or other non-SSRI antidepressants {16,17}.

Against this background we report the findings from a double-blind randomised crossover trial of sertraline and reboxetine in healthy volunteers. This was aimed at exploring modes of action of antidepressant drugs on levels of wellbeing and in particular the serenic effect that appears associated with the use of SSRIs which may mediate their therapeutic effect.

Methods

Twenty healthy volunteers aged between 28 and 52, with a mean age of 37.8 years, were recruited to a study comparing reboxetine with sertraline on a range of personality, self-report and quality of life measures. The study was aimed at establishing the effects of antidepressants on levels of wellbeing in subjects not currently depressed. There were 9 males and 11 females recruited from among the administrative, medical and nursing members of the North West Wales district general hospital psychiatric unit, as well as four others known to members of the unit. Ethical permission had been obtained from the North West Wales Ethical Committee. Written consent to inclusion was obtained from each subject. All volunteers were free of medical conditions. None were on concurrent drug treatment. None had a history of previous psychiatric illness. The two volunteers whose experiences are reported here have given consent for this information to be reported.

Subjects were randomised to reboxetine, a selective noradrenaline reuptake inhibitor, or sertraline, a selective 5HT reuptake inhibitor, in a crossover design so that a proportion received reboxetine for two weeks followed by a two week drug free period and thereafter sertraline for two weeks or alternatively sertraline followed by reboxetine. The dose of the drugs was either 4mgs of reboxetine for the first five days of the reboxetine arm with an option to increase to 4mgs bd if tolerated or sertraline 50mgs for the first five days of the sertraline period with an option to increase to 50mgs bd if tolerated.

At baseline, subjects completed a Karolinska Personality Questionnaire {18}, a Tridimensional Personality Questionnaire {19}, a Profile of Mood States (POMS) {20}, a Positive and Negative Affect Scale (PANAS) {21}, a Social Adaptation Self Evaluation Scales (SASS) {22} and a BIS-BAS scale {23}. The effects of both drugs in the whole group on mood scales, personality inventories, side effect rating scales and other measures will be reported elsewhere

POMS, PANAS and SASS scales were completed on a daily basis as well as a daily diary of impressions of the functional and physical effects of each drug. Volunteers were actively encouraged to consult their partners or others as to any changes that these others noticed in them over each two-week period. A focus group was conducted at the end of the study aimed at establishing whether there were effects characteristic of either drug. All ratings were done blind. The blind was only broken two weeks after the study was completed.

Results

A preliminary analysis of the results indicates that two-thirds of subjects responded to one or other of the two drugs but not the other with a 'better than well' response. Response appears to have been predicted by personality factors similar to those outlined by Joyce in a study of depressed subjects randomised to either relatively selective noradrenergic or serotonergic reuptake inhibitors {24}. The group also showed changes on the KSP that have been reported in depressed patients following SSRIs {25}. Finally in the group as a whole a greater number of subjects expressed a preference for sertraline than for reboxetine.

When on reboxetine, two subjects reported becoming depressed. In both cases they likened the experience to post-childbirth baby-blues. Neither of these two subjects or any other subject while taking reboxetine had suicidal ideation. In contrast, two subjects taking sertraline developed clear suicidal ideation, one of which reached extremely serious proportions. Both these individuals appear to have had elements of akathisia and emotional blunting but other subjects had either akathisia or emotional blunting without becoming suicidal. We report on these cases in more detail, reconstructing events from the diaries kept by both subjects.

Case A

The first case was a 30 year old woman. She was randomised to reboxetine initially. This made her conspicuously relaxed and slightly sedated on the first day. She described the effect as a chill pill. In subsequent days she found normally stressing events less stressful. She described the effect as keeping her normal temperamental self on the straight and narrow. She had poor sleep but was uncertain if this was owing to childcare or the drug. During the two weeks on what turned out to be reboxetine, she reported dry mouth, sleeplessness, reduced appetite, nausea and constipation, which she attributed to the drug.

After randomisation to sertraline, within the first few days she appeared to become avoidant. She complained of a stiff jaw (an extrapyramidal side-effect, some variant of which was reported in 45% of the group while on sertraline). She had a migraine, which she did not attribute to the drug, along with nausea, malaise, restlessness, agitation, anxiety, vivid emotions, racing thoughts and ruminations, which she did attribute to the drug.

From the end of the first week she was reported by colleagues to be somewhat restless and fidgety. To some she appeared akathisic but not

so clearly that everyone would notice. She recognised her restlessness and had found that with a degree of concentration and fiddling she could disguise the effect. She also noted other changes in herself that she could not initially clearly describe.

In view of the side effects up to this point, the blind guesses of study monitors taking into account both drugs were that she was on reboxetine rather sertraline. She was noticed by the monitors by the end of the first week to have become needy of time and company. There were moments when she appeared to become preoccupied and emotional but on questioning would mention that she would be well in a short while, as her mood had been swinging 'one minute doom and gloom the next sunshine and laughter'. Toward the end of the first week on treatment, her diary records, and she reported to a study monitor, two incidents involving quite atypical behaviour for her. She reported a lack of guilt about something she was concerned she might be guilty about when she came off the medication and was herself. This as it turned out was the case.

Over the first weekend she had a nightmare about having her throat slit, so that it gaped open and she bled to death in the bed. She didn't get back to sleep. She did not increase the dose of sertraline over the weekend. Versions of this nightmare recurred on two succeeding nights.

At the start of week two, she remained restless, withdrawn and preoccupied. The possibility of halting the drug was raised but she opted to carry on, despite feeling as though she had a combination of bad PMS and pre-exam nerves. Her diary records that she thought she might have an infection that was aggravating things and a hope that when that cleared she would feel better.

By Wednesday, she had become withdrawn, was ruminating over impulsive, disinhibited things she had done, was tearful and not herself. She had very obvious restlessness of her legs. She said that she was not doing much work, that she couldn't cope with anyone's emotions and she tried to occupy herself by doing paper work but found it difficult to focus her attention. She described swings of emotion, with misery predominating but she was not depressed. She was advised to stop the drug and agreed to do so. She did not stop. In retrospect, it was almost as if she could not stop herself from taking the tablets. A number of other disinhibited things happened including telling her life history to a colleague, whom she did not know well, leaving him concerned.

Her diary records impulsiveness, irritability, over-sensitivity as well as marked suspicion. It also records a sense that she had an 'old me' and another. The other was like a bit of her childhood self, easily moved to emotion, simplistic, aware of social etiquette but not inclined to follow it, impatient, selfish and irresponsible. The 'old me' could only watch what was happening and was helpless to stop the other bit which was in control.

The following day it turned out she had not stopped the tablets and the medication was discontinued by study monitors. She looked unwell but seemed to be making a great effort at trying to appear normal. She was still akathisic, at a level that would be apparent to most observers. That night she was seriously suicidal, although the tablet she was due to take that night had been stopped.

On the Friday she telephoned early in the morning, distressed and tearful after the previous night. Her conversation was garbled. She described almost going out and killing herself. She was visited at home. She recounted that the night previously she had felt complete blackness all around her. All she could focus on was the pen and the questionnaire in front of her but she couldn't write anything down. She felt hopeless and alone. It seemed that all she could do was to follow a thought that had been planted in her brain from some alien force. She suddenly decided she should go and throw herself in front of a car, that this was the only answer. It was as if there was nothing out there apart from the car, which she was going to throw herself under. She didn't think of her partner or child. She was walking out of the door when the phone went. This stopped the tunnel of suicidal ideation. She later became distraught at what she had nearly done and guilty that she had not thought of her family.

She was taken for a walk and appeared to gather herself. Later in the day she completed a diary entry for the night before to supplement the brief entries of the previous day, which included a hope that she would make it through the night. In this she described being jumpy, anxious and suspicious. Her mind was racing and spiralling out of control. Then it went blank except for the clear thought that she must kill herself violently by throwing herself beneath a car or train. This clear thought appeared irresistible and its appearance seemed to put an end to the anxiety. It was trance-like and only broken by a phone-call, which came when she was felt she was about to act on the basis of this idea.

Contact was maintained over the weekend. By the Monday she declared herself to be back to herself. She looked better but remained vulnerable and was clearly apprehensive about talking about what had happened. Both study monitors and the research subject were still blind at this point as to the identity of the medication. The subject herself remains very disturbed at what has happened.

During this period daily POMS and PANAS ratings were undertaken. On the POMS the words most consistently endorsed were lively, active, cheerful and vigorous during the reboxetine block. On sertraline, especially in the second week, the words endorsed were tense, worn out, unhappy, fatigued, sad, confused, shaky, discouraged, on edge, miserable, bewildered and nervous were regularly endorsed. On the PANAS, she had a mean positive word score of 19.7 in week one and

20.3 in week 2 on reboxetine, and 25.3 in week one on sertraline falling to 19.4 in week 2. Her negative word score was 10 in week one on reboxetine, 11.4 in week two, rising to 12.7 for week one on sertraline and 22.9 for week two.

Case B

B was a 28-year old woman at the time of entry to the study. She had no history of psychiatric or medical problems. She smoked and took approximately two units of alcohol her week. Her only significant period of stress was three years previously when she separated from a partner. At that point in time the thought of suicide had crossed her mind but without any intent, plans or active ideation of any sort.

She was randomised to reboxetine followed by sertraline 50mgs for five days increasing up to 100mgs. On reboxetine at some point during the two weeks, she suffered from sleeplessness, constipation, dry mouth with some reduction of appetite, sexual dysfunction and impairment of concentration. In general, however, she found herself more confident, calm and energetic.

On going on sertraline she noticed the following effects, which she attributed to the drug: nausea, lethargy, malaise, panic and pain in her jaw. Within two days she also noted in her diary that she had become snappy and much more likely to say things that came to mind and that this had been noticed by her colleagues. By the third day, she records herself as more assertive. She also reported her mood as liable to drop, that generally her emotions were liable to swing, that she was sluggish, that she had become irritable at the slightest little thing and was liable to take comments personally. Her mood does not appeared to have been depressed but colleagues noted her swings from cheerfulness to withdrawal.

She also found herself restless and reported that she didn't know if she was 'coming or going'. This did not appear to be an obvious akathisia but most probably was, as she endorsed agitation as a side effect of the drug. Close colleagues and her mother noticed this and other disinhibited events of the kind described below. All agreed that she was adversely affected by the second pill and she was advised particularly by her mother never to go on anything like that again.

There was a reluctance to mention any of this to others and only a brief mention in a post-study focus group led to a subsequent discussion in which these details became clear. One of the intriguing features of this woman's experienced endorsed by Case A was a concern that elaborating on what was happening her would lead to others thinking she was crazy – no-one had warned her beforehand that this could possibly happen on this drug. Her diary entries and her rating scales were therefore economical with the truth.

While on reboxetine on the POMS, this subject endorsed the words worn out, and weary during the first two weeks, switching to sad, annoyed, miserable, unhappy and angry during week two. On the PANAS her positive scores dropped from 17.6 and 15.4 on reboxetine to 11.4 and 12.6 on sertraline. Her negative scores did not change. However, there is a group of over 6 co-habitees, work colleagues and study monitors who had become aware of the changes listed above and below.

B, briefly in her diary and at greater length subsequently, described finding herself in a state where she didn't think through the consequences of what she did or said. She didn't appear to feel afraid. For example, on one occasion while driving home with her mother in the car a group of 18 year old boys by the side of the road made obscene gestures and shouted at them, while the car was moving slowly at a tricky juncture in the road. She stopped the car in the middle of moving traffic, went over to them and grabbed one of them, telling him if he did anything like that again she would 'deck' him. She came back to the car to find her mother extremely frightened about what had happened. There was a contrast between reboxetine and sertraline in this regard in that reboxetine had made her feel calm but in a manner that left her still able to feel fear. In contrast on sertraline, she felt aggressive and fearless. She found herself thinking on several occasions when faced with situations with people that she could 'deck' them.

She increased her dose of sertraline to 100 mg as per protocol. Thereafter she felt worse, so that she reduced the dose back to 50 mg three days before the end of the study. Following the increase in dose, she had two disturbing nocturnal episodes on consecutive nights. She is a woman prone to lucid dreaming and both sleep walking and sleep talking with extensive memory the following day for what has happened the previous night. Her partner regularly reports her as being awake during these episodes. It is difficult therefore to determine what happened but her recollection is, while awake or lucidly dreaming, that she spent a long period lying in her bed fantasising about hanging herself from a beam across the bedroom ceiling. She was aware that these thoughts were accompanied by an abnormal lack of concern as to whether her partner, mother or others might find her. She is not aware of ever having comparable thoughts before. The reason she did nothing she explained afterwards was because she was a coward and had a vestigial concern about being found by her son. This episode repeated itself the following night.

There was a strong feeling that while on the drug in some way she was being controlled and that suicide might happen. She rationalised that she had only a few days left on the drug and was probably therefore safe to continue, particularly with the dose reduction. The feelings cleared to some extent on the lower dose and cleared completely after the drug had been discontinued. In her opinion had the drug been continued for longer in a situation where she was a patient seeking help rather

than a volunteer who could discontinue the drug, that there might have been an up to 50/50 chance of a self harm episode happening.

A final point of note about this case is that the subject was aware afterwards of perceptions that the 'instability' she had shown on the drug would reflect on her. She would be thought to be unstable rather than to have had a drug-induced instability. Both subjects felt this. They are almost certainly accurate to some extent.

Discussion

These cases, which emerged in the course of a blind controlled study, shed new light on the issue of drug induced suicidal ideation. Hitherto one of the arguments of the sceptics has been that depression leads to suicidal ideation and against this background it is difficult to make a causal connection between antidepressant intake and suicidal ideation {25}.

The example of reserpine is of interest here. Reserpine, a psychotropic drug with RCT evidence of antidepressant efficacy, was associated with an emergence of suicidal ideation and a number of completed suicides during the 1950s when it was widely used. At the time, it was argued that it must be triggering a depressive disorder. A recent reanalysis of these early studies suggests that in fact it precipitated akathisia and this many have mediated the suicidality {26}. Of particular interest, is the fact that the problems and suicides occurred in non-psychiatric patients being treated with reserpine for hypertension, permitting a strong causal claim to be made.

In a recent healthy volunteer study involving randomisation to droperidol, lorazepam and placebo, we also witnessed an emergence of suicidality that appeared to be linked to agitation or akathisia {27}. This antidepressant study provides support for the argument that psychotropic drugs in certain circumstances may induce a suicidality that would otherwise not have happened.

The cases described in this paper appear to have become suicidal on sertraline with no easy means of explaining what happened other than by invoking an SSRI-induced suicidality. The mechanism through which this was mediated appears to have been a combination of akathisia and emotional blunting, as well as other features suggestive of an automatism. The 'disinhibition' reported appears comparable to that reported by Hoehn-Saric *et al.* {28} on fluvoxamine and fluoxetine. To date, the phenomenology of what can happen has not been explored in any detail. It is notable that neither drug-induced depression nor drug-induced akathisia experienced alone necessarily led to suicidality in this study. Indeed in the case of the two volunteers who became suicidal, they do not seem to have been depressed.

One of the messages of the reserpine story appears to have been that those who did not suffer from a psychiatric illness may have been at more risk from this drug than others. This healthy volunteer study suggests that individuals who are not frankly depressed may also be at increased risk of drug-induced problems compared to others. Concomitant drug prescription may in fact in many cases minimise the risks. Given that antidepressants are commonly prescribed for stress reactions, particularly when given alone, this point would seem to be of some importance.

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