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RISPERIDONE IN CHILDREN AND ADOLESCENTS WITH AUTISTIC DISORDER AND AGGRESSIVE BEHAVIOUR

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Introduction

Autism is characterised by impairment of reciprocal social interaction, abnormalities of verbal and non-verbal communication, and repetitive stereotyped routines (Rutter and Schopler, 1992). In addition, learning disabilities (mental retardation) can occur in up to 85% of autistic individuals (Nass and Koch, 1992). The disorder has a wide range of clinical presentations, which significantly impact on lifestyle including repetitive thoughts, ritualistic behaviours and social withdrawal. However, one of the most problematic features is aggression where the severity is not in proportion to the precipitant (Horrigan and Barnhill, 1997).

Traditionally, behavioural methods have formed the mainstay of treatment (Rutter, 1985). Promotion of normal development, reduction of rigidity and stereotypes, and removal of maladaptive behaviour can be achieved with conventional management techniques, such as operant conditioning and shaping, and by more sophisticated approaches like the Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH) programme (Van Bourgondien *et al*., 1992).

Until recently, psychotropic drugs have had a limited role in the treatment of autism, usually in the management of the more severe aggressive symptoms. The most consistently effective drug treatments for patients with autism and related pervasive development disorders have been those that have targeted central dopamine and serotonin systems. These neurotransmitters have been shown to be dysregulated in some patients with autism and studies have demonstrated raised levels of the dopamine metabolite, homovanillic acid, in the cerebral spinal fluid of autistic adults and elevated blood

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serotonin concentrations in children with the disorder (Gillberg *et al*., 1983; Cook and Leventhal, 1996; McDougle *et al*., 1996a). Typical antipsychotics, such as the dopamine antagonist, haloperidol, have been effective in reducing many of the maladaptive behaviours but often at the cost of acute and extrapyramidal side effects (Anderson *et al*., 1984; Campbell *et al*., 1997). Reduction in repetitive behaviour and aggression, and elevation of some elements of social behaviour have been seen more recently with serotonin reuptake inhibitors e.g. clomipramine and fluvoxamine (Gordon *et al*., 1993; McDougle *et al*., 1996b).

Risperidone, an atypical antipsychotic, is a potent antagonist at serotonin$_{2A}$ and dopamine D_2receptors (Leysen *et al*., 1994). Indirect preclinical and clinical evidence supports the use of risperidone to treat impaired social behaviour, interfering repetitive phenomena and aggression (McDougle *et al*., 2000). In addition, its serotonin to dopamine ratio of receptor blockade appears to produce a lower risk of acute and chronic extrapyramidal side effects as well as enhanced efficacy for the 'negative' symptoms of autism than typical antipsychotics (Möller *et al*., 1991). A double-blind, placebo-controlled study of risperidone in adults with autism subsequently found risperidone to be more effective than placebo in the short-term treatment of symptoms (McDougle *et al*., 1998). However, evidence for its clinical effectiveness in children is limited to open-label trials (Findling *et al*., 1997; McDougle *et al*., 1997; Perry *et al*., 1997; Nicolson *et al*., 1998).

The following case series details children and adolescents who have been admitted to and/or treated in a specialist in-patient facility for children with learning disability and psychopathology. Admission to this unit is considered only when all available community treatments have been unsuccessful in alleviating symptoms. These reports contribute to the emerging evidence that risperidone may be beneficial in the treatment of children and adolescents with autistic disorder.

Case Reports

Case 1

T is a fourteen-year-old boy with Down's syndrome. He has the obvious stigmata of Down's syndrome and mild sensory-neural deafness but none of the physical abnormalities often associated with this condition. He lives with his parents and older sister. From a very young age he was significantly delayed in reaching developmental milestones. He did not walk until the age of two or speak his first word until five, and attended a special school throughout childhood. Psychometric assessment confirmed a moderate learning disability.

He was first seen by the Community Learning Disability Services at five years of age, when his behaviour at home and at school was cause for concern and he presented a more consistent management problem to his family. In particular, his mother had lost all confidence in her ability to cope. Outbursts of verbal and physical aggression and wilful destruction of property occurred frequently particularly when his routine was interrupted or when he was asked to carry out tasks that he objected to. He lashed out at those in authority, his sister and other children, and required one-to-one attention at home and school.

T responded somewhat to the discipline of schooling with fewer violent outbreaks. However, behavioural interventions that focused on manipulation of

antecedents and consequences of his actions were thwarted by his poor attention span and also by some degree of parental inconsistency. Ritualistic behaviour emerged as he grew older, particularly associated with light switches and electrical plugs, and up to an hour was often spent turning lights on and off. By the age of 12, all community treatment options had been exhausted and T was admitted to a special hospital unit for children with learning disabilities. His behaviour was uncontrollable and so disruptive that he was considered unsuitable to continue community schooling. There followed a period of overall assessment and T's score of 35 on the Childhood Autism Rating Scale placed him at the upper limit of 'moderate'(Schopler *et al*., 1980). Repeated mental state examinations showed no evidence of overt psychotic phenomena.

In the early months on the unit, the severe nature and extent of his aggression became evident and deficits in his social skills were obvious especially when he participated in unstructured play sessions. He responded slowly to the structured environment, a consistent approach and to a TEACCH programme (Van Bourgondien *et al*., 1992), and gradual reintegration into school occurred concurrently after a period of six months. However, although he initially coped very well, his behaviour regressed over time.

Antipsychotic therapy was considered when T was 13 years old. Risperidone was started at a dose of 0.25mg daily with weekly incremental increases of 0.25mg. There was little change in T's behaviour preceding a dose of 1mg daily. However, at 1.5mg and 2mg a day, significant improvement was evident; aggressive outbursts were fewer and less severe, and ritualistic behaviour was much less remarkable. This change allowed him to spend less time on the unit and more time at home and at school, achieving good progress reports from all carers.

After six months of risperidone therapy, T's parents were eager for him to return home permanently and attend school full-time, and this was successfully implemented over a one-month period. His teacher noted that he had become much more friendly and popular with his peers, and that he now joined in activities with other children, enjoying the fun and games. He evidently responded to being taken by the hand and to praise on completing tasks.

Over the past 20 months, T appears to have done well on risperidone and is currently maintained on 2mg risperidone a day. He has had no adverse effects of treatment. He is more settled and only has occasional aggressive outbursts, which are mostly verbal, cause little disruption and are easily managed with diversionary techniques.

Case 2

K was born in 1986 and suffers from autistic disorder, severe learning disabilities and epilepsy. His development was significantly delayed and before the age of two his behaviour was aggressive, particularly towards his parents and siblings, and characterised by biting and kicking.

He was referred to the Learning Disability Psychiatry Services at the age of seven for assessment by a team of clinical psychologists. Autistic disorder was diagnosed following long periods of behavioural observation in different settings. As most of his aggressive outbursts were precipitated by disruption to his routine, behavioural treatment strategies were implemented but with little success. Increased aggression and disruptiveness prompted an urgent domicilary visit. He

had begun to smear faeces around the home and classroom and there were reports of inappropriate sexual behaviour, including touching his classmates' genitals and fondling his mother's breasts. He had also begun to demonstrate rigid behavioural traits, particularly regarding food. Up to three hours would be spent over a meal, arranging and re-arranging food on the plate. Food was refused unless cooked as he preferred and he was highly selective in his choice. His parents felt that they were no longer able to cope and K was admitted to the children's unit of a hospital specialising in learning disabilities.

Throughout his childhood K had frequent complex partial seizures with secondary generalisation. Electroencephalography showed a focus in the right temporal lobe. Carbamazepine 700mg daily and sodium valproate 1200mg a day were prescribed and by the age of 12 he had good seizure control. There was no apparent direct relationship between the epilepsy and behaviour, and seizure control made no obvious impact on his behaviour. K has been seizure-free for 15 months, and his antiepileptic drugs and their doses have remained unchanged during this time.

His hospital stay, which was interspersed with frequent home leave, lasted 10 months. His disruptive behaviour responded to the structured environment of the special unit and to specific treatment approaches based on reinforcement of appropriate behaviour. He became less aggressive although there was no change in his preoccupation with food. Pharmacological interventions were also introduced at this time. To begin with Vallergan® 10mg twice daily was prescribed for its sedative properties. However, after six months this was changed to thioridazine 10mg a day, rising to 30mg a day, which had some initial calming effect although it was not sustained. Assessment of his mental state revealed nothing to suggest a concurrent psychotic process.

With assistance from respite services and intensive support from community nursing and psychology services, K's family adapted to his challenging behaviour. However, as he grew in physical stature, his behaviour, where once disruptive, became a threat. As a consequence, at the age of 15, risperidone was started at a low dose of 0.5mg daily and increased to 0.5mg twice daily after two weeks. Within a month there was a significant change in his behaviour, he was much calmer and more sociable. Although he continued to display some rigidity at mealtimes, it was unremarkable when compared with that a few weeks previous. He was more easily distracted and would eat his meal in 20-30 minutes. He began to attend the local youth club, and teachers and care-workers commented on the overall improvement in his level of performance, especially in his attention and ability to concentrate.

Over the last 15 months, since the introduction of risperidone, K has only had two outbursts of physical aggression, both while on holiday and away from his routine environment, and both short-lived and self-limiting. He continues to be maintained on 0.5mg twice daily and tolerates risperidone well, showing no evidence of adverse effects.

Case 3

D is a 14-year-old boy with a diagnosis of severe learning disability and autistic disorder. He was referred to the Learning Disability Services at the age of three with behavioural difficulties including nipping and kicking, climbing, a fascination with fire and a high activity level. He had marked communication problems. An as-

sessment with the Autistic Screening Instrument for Educational Planning (Krug *et al.*, 1980) confirmed severe autism with marked deficits in language and social interaction.

Over the next two years the community learning disability nurse and consultant clinical psychologist worked intensively with D, his family and school but his response to behavioural approaches was minimal. An additive free diet under the direction of a dietician also had no apparent benefit. He was extremely active, continuously jumping and running around. He would scream in a high pitched voice but had no useful speech. He had a fascination with electrical sockets and the television, and would spend long periods tapping panes of glass. In view of his severe and worsening behavioural problems when aged five, D was taken out of school and admitted to a children's unit of a hospital specialising in learning disabilities for further assessment and treatment.

Thioridazine was introduced at 10mg daily and gradually adjusted to 50mg daily but his response to this therapy was very limited. With direct observation of D's behaviour, it became clear that he was suffering from periods of impaired consciousness lasting between 30 and 60 seconds, during which he had repeated hand movements and eye flickering. A clinical diagnosis of complete partial epilepsy was later confirmed with electroencephalography. He was treated with carbamazepine, increasing to 600 mg daily, and within six months overt seizure activity was no longer evident. He has not had seizures since and remains on this treatment. The successful treatment of his epilepsy had no impact on D's behaviour, and a direct association between seizure activity and challenging behaviour was not apparent.

Behavioural techniques were employed throughout his admission to assist in his management but, as before, these had little effect. When he was eight, he was given methylphenidate up to a dose of 15mg daily although this too was of no benefit.

The severity of D's learning disability and paucity of verbal communication made assessment of his mental state difficult, but there was no evidence to suggest affective disturbance or hallucinatory phenomena.

At the age of 12, thioridazine was discontinued and risperidone was started at a daily dose of 0.5mg and upwards titrated to 2mg daily over 6 weeks. Improvement in D's behaviour was evident by a reduction in his activity level after about three weeks. Over the following 10 weeks risperidone was increased to 4mg daily and he became increasingly settled. He squealed less frequently and was calmer, his concentration improved and he was toilet trained. His behaviour was considered sufficiently controlled to allow him to reconvene lessons at the community school.

D has been able to spend more time out of hospital and currently lives at home for four days a week. After two years of risperidone treatment he continues to maintain his improvement on 4mg a day, which he tolerates well. He is also taking carbamazepine 600mg daily for control of seizures. Episodes of over activity still occur but these are fewer and less sustained than previously. His current total score on the Childhood Autism Rating Scale is 44.5, signifying that he is still severely autistic.

Case 4

R, a 17-year-old teenager with severe autistic disorder, moderate learning difficulties and epilepsy, lives with his parents

and younger sister. His family was first concerned about his development when he was one year old. He did not walk until the age of three and not until five did he begin to utter a few words albeit unintelligibly. A consultant clinical geneticist found no cause for his learning difficulties although he has always needed special schooling. At the age of eight, R began to have nocturnal seizures. Primary generalised epilepsy was diagnosed, which was successfully controlled using sodium valproate 800mg daily.

At 13 years of age he was referred to the Community Learning Services with difficulties in concentration, explosive outbursts especially when his routine was interrupted, and episodes of wailing for no apparent reason. He was also preoccupied with routines, had no concept of time, spent long periods staring at his hands and displayed ritualistic hand movements. R was sent to a consultant clinical psychologist for behavioural assessment although subsequently use of behavioural modifying techniques had little effect.

R was referred again to the Community Learning Disability Services aged 16. Repetitive behaviours were prominent and associated with outbursts of aggression particularly directed towards his mother. Pharmacotherapy was considered and risperidone was started at 1mg daily. An improvement in his conduct was noted within a few days and he became much more relaxed and less preoccupied with routines and rituals. He was able to make decisions more easily and to tolerate changes in his routine and environment to the extent that he enjoyed a holiday abroad.

Risperidone is currently prescribed at a dose of 1.5mg daily and there has been consistent improvement in his behaviour since its introduction 18 months ago. Furthermore, the dose of sodium valproate has been reduced to 600mg daily as R has not had seizures for over two years. With the exception of some weight gain, R has had no other side effects of risperidone treatment. During the first six months of treatment he gained 5kg but, thereafter, his weight stabilised and has been so for about one year.

Discussion

Where clinical trials provide information on the overall effects of a treatment on a patient population, they usually do not detail the specific effects on the individual and their way of life. These case studies describe risperidone treatment in children and adolescents with autism where previous reports have described risperidone's effectiveness in this disorder in infants (Posey *et al*., 1999), adults (McDougle *et al*., 1995, 1998; McCartney and Calvert, 1999) and open label trials (Findling *et al*., 1997; Horrigan and Barnhill, 1997; McDougle *et al*., 1997; Perry *et al*., 1997; Nicolson *et al*., 1998). Seizure disorders are not uncommon in those with autistic disorder (Volkmar and Nelson, 1990) and this report includes three patients with comorbid neurological conditions.

The cases detail the successful treatment of aggressive behaviour with risperidone in children and adolescents with autism. The youngsters had severe problems with aggression and social relatedness. Their psychiatric symptoms were unimproved with non-pharmacological interventions alone and unremarkable with the medications prescribed. Risperidone significantly reduced symptoms possibly allowing psychosocial therapies to have more effect. The significant improvements in these individuals

mirror those reported (Findling *et al*., 1997; Horrigan and Barnhill, 1997; McDougle *et al*., 1997).

One of the most common presenting problems was aggression. Risperidone effected a significant reduction in aggressive behaviour and explosive outbursts, noted by parents, teachers and care-workers. This decrease in aggression has been noted in individuals with autism and pervasive developmental disorders (Horrigan and Barnhill, 1997; McDougle *et al*., 1997; Nicolson *et al*., 1998). Improvements were also apparent for other problematic behaviours including overactivity, social withdrawal and repetitive stereotyped behaviour. Although it has been suggested that obsessive-compulsive behaviours may be increased in adults with schizophrenia (Kopala and Honer, 1994; Dodt *et al*., 1997), interfering repetitive behaviours have been found to improve with risperidone in adults (Purdon *et al*., 1994; McDougle *et al*., 1995, 1998; McCartney and Calvert, 1999) and children (McDougle *et al*., 1997) with autism and pervasive developmental disorder accompanied by mental retardation.

The functioning of these youths was also better after risperidone therapy. Where they had been taken out of community schooling because of their aggression and disruptiveness, they were able to return. Parents and teachers observed that they were more likely to participate in activities with their peers than before and also able to concentrate on set tasks.

Side effects of risperidone reported in children and adolescents include sedation, weight gain, galactorrhea and extrapyramidal symptoms (Mandoki, 1995). In this latter study, risperidone was increased by 0.5mg twice daily to doses of up to 8mg a day. The low incidence of side effects seen in this series may have been the result of dose titration occurring slowly over several weeks and also to the low doses at which treatment was initiated and found to be effective. While some weight gain was noted in one patient, no other side effects including extrapyramidal symptoms were noted. Extrapyramidal symptoms are often found in autistic children using conventional antipsychotics (Campbell *et al*., 1997) and that they were not noted with risperidone here or by others is an important observation (Casaer *et al*., 1994; Hardan *et al*., 1996; Horrigan and Barnhill, 1997; McDougle *et al*., 1997; Nicolson *et al*., 1998). Our findings are consistent with accounts of the favourable side effect profile of risperidone in adults (Marder and Meibach *et al*. 1994; Owens, 1994) and are also supported by reports in children (Simeon *et al*., 1995; Sternlicht and Wells, 1995; Hardan *et al*., 1996).

This case series is limited by the small number of patients, unblind nature of the observations, absence of standardised scales for assessing symptom change, and lack of controls and drug-withdrawal design. However, the apparent positive response to treatment, and that risperidone was well tolerated in these youngsters with autism, reinforces the need to further evaluate the effects of risperidone in this patient population in large double-blind clinical trials.

Summary

Many patients with autistic disorder and learning disabilities show aggressive behaviour. This case series describes the use of risperidone in the treatment of four children/adolescents with autistic disorder who presented with severe and persistent symptoms of aggression and irritability that had remained treatment unresponsive. In addition, all patients had learning disabilities, one had Down's syndrome and three had epilepsy. Riperidone was initi-

ated at 0.25mg or 0.5mg and titrated upwards slowly until maximum clinical benefit. Significant changes in social interaction, repetitive stereotype routines and aggressive behaviour were observed between a few days and up to four weeks after the start of treatment. The youngsters continue to improve on low maintenance doses of between 1-4mg a day. Treatment was well tolerated and although weight gain was seen in one patient none of them experienced extrapyramidal side effects. These case reports contribute to the emerging evidence that risperidone may be effective in ameliorating dysfunctional behaviours in children and adolescents with autistic disorder.

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