HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol. Clin. Exp. **13**, 575–577 (1998)

Rhabdomyolysis Without Neuroleptic Malignant Syndrome Induced by Additional Treatment of Risperidone

NORIO YASUI[1], TSUYOSHI KONDO[1]*, KOICHI OTANI[2] and SUNAO KANEKO[1]
[1]*Department of Neuropsychiatry, Hirosaki University School of Medicine, Hirosaki 036, Japan*
[2]*Department of Neuropsychiatry, Yamagata University School of Medicine, Yamagata 990-23, Japan*

This is the first case report of rhabdomyolysis without neuroleptic malignant syndrome induced by additional treatment of risperidone. The manifestations of this side effect were symptoms of myalgia, muscle weakness and red-coloured urine with findings of markedly elevated levels of creatine kinase and myoglobin in serum as well as myoglobinuria. Early diagnosis of rhabdomyolysis, immediate discontinuation of risperidone and administration of dantrolene had favourable effects on the course of the treatment of this side effect. © 1998 John Wiley & Sons, Ltd.

KEY WORDS — rhabdomyolysis; risperidone; creatine kinase; myoglobin

INTRODUCTION

Rhabdomyolysis is a potentially lethal syndrome resulting from traumatic and nontraumatic skeletal muscle injury that alters the integrity of the muscle cell membrane sufficiently to allow the release of the muscle cell contents into the plasma (Poels and Gabreëls, 1993). The clinical signs and symptoms of rhabdomyolysis are muscle pain and weakness and dark red-coloured urine. The diagnosis of rhabdomyolysis is confirmed by the findings of increased levels of creatine kinase (CK) and myoglobin in serum (Jermain and Crismon, 1992; Poels and Gabreëls, 1993). Rhabdomyolysis is more likely to occur in psychiatric patients with risk factors, e.g. neuroleptic malignant syndrome (NMS), overdose medication, agitation, dehydration and intramuscular injection (Jermain and Crismon, 1992).

Risperidone is a benzisoxazol-derivate with a potent serotonin 5-HT_2 and a milder dopamine D_2 antagonistic activity (Schotte *et al*., 1995). It has been reported that risperidone has less extrapyramidal symptoms than haloperidol when given at recommended doses (e.g. risperidone 6 mg versus haloperidol 20 mg) (Marder and Meibach, 1994). Meanwhile, several case reports have showed risperidone-induced NMS accompanied by rhabdomyolysis (Raitasuo *et al*., 1994; Bonwick *et al*., 1996; Levin *et al*., 1996). However, to our knowledge, there has been no report suggesting risperidone-induced rhabdomyolysis without NMS or extrapyramidal symptoms. Therefore, this is the first case report of rhabdomyolysis irrespective of NMS during risperidone treatment.

CASE REPORT

The case was a 47-year-old male inpatient diagnosed as catatonic type schizophrenia according to DSM-IV (American Psychiatric Association, 1994). He had been treated with intramuscular haloperidol decanoate 100 mg monthly and oral administration of 150 mg/day of mosapramine, an antipsychotic drug, of which pharmacological property is characterized by higher affinity ratio 5-HT_{2A}/D_2 than haloperidol and lower than risperidone (Schotte *et al*., 1995), together with biperiden 6 mg, diazepam 10 mg and flunitrazepam 8 mg daily for the past 4 years. The plasma concentrations of haloperidol had ranged from 3·0 to 5·0 ng/ml. However, his psychotic symptoms acutely deteriorated, showing agitation, bizarre behaviours and auditory hallucinations. Thereafter, mosapramine 150 mg/day was replaced with risperidone 6 mg/day, and other remaining drugs were maintained at the same doses. On the 11th day after the introduction of risperidone, haloperidol decanoate 100 mg was intramuscularly injected as

*Correspondence to: T. Kondo, Department of Neuropsychiatry, Hirosaki University School of Medicine, Hirosaki 036, Japan. Tel: +81-172-39-5066. Fax: +81-172-39-5067.

CCC 0885–6222/98/080575–03$17·50

usual. The plasma concentration of haloperidol was 6·0 ng/ml on that day.

On the 15th day after risperidone treatment, the patient complained of muscle pain and weakness in both legs and red-coloured urine. On the 16th day muscle pain and weakness spread over whole body. Body temperature was 37·5°C, blood pressure 116/74 mmHg and heart rate 96 bpm. Pulmonary, cardiovascular and abdominal exams were all normal. Neither extrapyramidal symptoms nor autonomic symptoms were observed. The laboratory findings were as follows: white blood cell count 10 500/ml, CK over 20 000 IU/L, creatinine 2·1 mg/dl, blood urea nitrogen 33 mg/dl and uric acid 11·9 mg/dl. Urine examinations revealed myoglobinuria, pigmenturia and proteinuria. The diagnosis was rhabdomyolysis. Since risperidone was regarded as the most causative drug for this side effect, it was immediately discontinued. Also, intravascular injection of dantrolene 40 mg/day and intensive hydration were initiated. On the second day after risperidone discontinuation, the laboratory findings were white blood cell count 7000/ml, CK 56 800 IU/L, myoglobin in serum 4050 ng/ml, lactate dehydrogenase 4030 IU/L, aspartate aminotransferase 1030 IU/L, creatinine 2·3 mg/dl, blood urea nitrogen 30 mg/dl and uric acid 9·2 mg/dl, respectively. The appearance of urine was still dark red. On the fourth day the urine colour became clear, although he still complained of muscle pain in both legs. The CK values were 19 690 IU/L in the morning and 14 230 IU/L in the evening. On the seventh day, clinical symptoms of rhabdomyolysis disappeared, and white blood cell count was 4800/ml, CK 3840 IU/L, myoglobin in serum 454 IU/L, lactate dehydrogenase 1092 IU/L and aspartate aminotransferase 124 IU/L. Dantrolene and hydration was terminated on the same day. All of the laboratory findings were normalized over 2 weeks after risperidone discontinuation. Haloperidol 6 mg/day was re-introduced orally 3 weeks after risperidone discontinuation since his psychotic symptoms again deteriorated. No clinical signs or symptoms suggesting the relapse of rhabdomyolysis were observed thereafter. The steady-state plasma concentration of haloperidol was 12·0 ng/ml on the ninth day after oral haloperidol administration had been started.

DISCUSSION

According to a recent review (Jermain and Crismon, 1992) and a case report (Marsh and Dolson, 1995) of rhabdomyolysis, haloperidol is considered to be one of the main causative drugs for rhabdomyolysis. In the present case, haloperidol decanoate was injected a few days before the onset of rhabdomyolysis. However, there had been no clinical signs or symptoms suggesting rhabdomyolysis for the past 4 years while haloperidol decanoate was being regularly administered. Furthermore, rhabdomyolysis did not recur by rechallenge of haloperidol by oral administration one week after rhabdomyolysis had disappeared, although the plasma concentration of haloperidol (12·0 ng/ml) was much higher than that just before the development of rhabdomyolysis (6·0 ng/ml). These clinical courses suggested that the causative drug for rhabdomyolysis in our case was unlikely to be haloperidol. Therefore, it is possible that risperidone itself induces rhabdomyolysis. Potent 5-HT_2 antagonistic activity of risperidone (Schotte *et al*., 1995) may be partly associated with the development of rhabdomyolysis, since the serotonergic system is suggested to be involved in some toxicity for skeletal muscle, leading to muscle necrosis (Meltzer, 1976; Narukami *et al*., 1991). As a result, an immediate discontinuation of risperidone as well as early diagnosis of rhabdomyolysis led to the successful recovery from this side effect in our case. However, as another possible cause for rhabdomyolysis, some pharmacodynamic interaction between risperidone and haloperidol cannot be excluded entirely.

The psychotic symptoms before administration of risperidone in this case, i.e. agitation, bizarre behaviours and auditory hallucinations, can be also observed as initial symptoms of lethal catatonia (Castillo *et al*., 1989). However, we did not find any other symptoms such as negativism, mutism, stupor, muscle rigidity or prominent autonomic symptoms, which were characteristic of typical lethal catatonia (Castillo *et al*., 1989). Furthermore, the psychotic symptoms rather ameliorated after the introduction of risperidone treatment. Therefore, the sequence of development of these symptoms including rhabdomyolysis can be distinguished from clinical course of lethal catatonia.

Meanwhile, risperidone-induced rhabdomyolysis previously reported (Raitasuo *et al*., 1994; Bonwick *et al*., 1996; Levin *et al*., 1996) was all associated with NMS. However, the present case did not develop any of the extrapyramidal symptoms, autonomic symptoms or high fever as the

diagnostic criteria for NMS requires (Levenson, 1985). Therefore, this is the first case of possible risperidone-induced rhabdomyolysis without NMS. Meltzer *et al*. (1996) recently reported two asymptomatic cases with increased serum CK levels after risperidone treatment. The increase in serum CK levels was observed 1–4 weeks after risperidone was administered. In the present case, rhabdomyolysis developed about 2 weeks after risperidone treatment. According to these findings, risperidone may have some harmful effects on skeletal muscle, which likely occur in a relatively early phase of the treatment. Therefore, careful monitoring of signs and symptoms of muscle damage should be taken into account within at least one month after risperidone treatment.

Rhabdomyolysis results from skeletal muscle injury that alters the integrity of the muscle cell membrane (Poels and Gabreëls, 1993). It has been suggested that the calcium homeostasis, i.e. the balance between the intra- and extracellular Ca^{2+} concentration is important for the integrity of the muscle cell (Poels and Gabreëls, 1993). Meanwhile, dantrolene is known to regulate the amount of Ca^{2+} released from the sarcoplasmic reticulam (Cedarbaum and Schleifer, 1990). In the present case, it is possible that dantrolene acted as a stabilizer to treat the impaired calcium homeostasis of injured skeletal muscle cells. Therefore, dantrolene probably has protective effects on skeletal muscle, and might be also effective in the treatment of rhabdomyolysis.

In conclusion, the present case developed rhabdomyolysis induced by additional treatment of risperidone to haloperidol, which was irrespective of the occurrence of NMS. Early diagnosis of rhabdomyolysis, immediate discontinuation of risperidone and adminstration of dantrolene had favourable effects on the course of the treatment of this side effect.

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