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***Rapid Communication***

# CAN RITODRINE HYDROCHLORIDE SUPPRESS THE BONE MARROW FUNCTION?

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## Introduction

Ritodrine hydrochloride (ritodrine) has been widely used as a tocolytic agent for many years. Although this drug is considered to be relatively safe for the patient, serious side effects, such as pulmonary edema and myocardial ischemia, have been occasionally reported. Recently, ritodrine-induced agranulocytosis has also been reported as another possible side effect of the drug[2)3)5)6)8)]. In the present study, we used the colony-forming unit-granulocyte-macrophage assay (CFU-GM assay) to clarify whether this drug could affect the bone marrow function in normal condition or not.

## Materials and Methods

Bone marrow was aspirated from 18 patients who admitted in our hospital due to hematological disorders, and a mononuclear cell fraction was separated by means of the differential centrifugation. The cells were washed and cultured in single soft agar layer at a concentration of $2\times10^5$ cells/plate using the colony assay technique[7)]. Ritodrine hydrochloride (Kissei pharm. Co., Ltd.) was added to the mononuclear cell suspension in final concentrations of 10, 100, or 1,000ng/ml, and the cells were incubated for ten days and then forming colonies were counted. Colonies with more than 40 cells were scored using an inverted microscopy. Four culture plates were prepared for each and CSF-"CHUGAI" (Chugai Pharm. Co., Ltd.) was added as a colony stimulating factor. Statistical significance was determined by Student's t test based on unpaired data. Statistical significance was assigned if $p<0.05$.

In formed consents were obtained from the patients beforehand.

## Results

Table 1 shows the effect of ritodrine on CFU-GM colony formation at various concentrations. The values are means ± standard deviations of the real numbers of colonies which were counted in different four plates. In our experiments, the mean colony count is 70±43 colonies per $2\times10^5$ cells plated as a control. When 10, 100, or 1,000ng/ml of ritodrine was added, the total number of colonies was 72±34, 68±36, and 67±36, respectively. There are not any significances in total numbers. In comparison

Table 1. Numbers of colonies in CFU-GM assay

| All cases | | Ritodrine (ng/ml) | | | |
|---|---|---|---|---|---|
| Sex | Age | 0 | 10 | 100 | 1,000 |
| Female | 34 | 121±11 | 118±9 | 107±12 | 109±5 |
| | 38 | 95±6 | 95±5 | 86±9 | 78±7 |
| | 39 | 53±5 | 97±7 | 93±6 | 98±5 |
| | 42 | 205±17 | 142±8 | 165±9 | 163±13 |
| | 42 | 30±4 | 30±3 | 30±3 | 29±5 |
| | 43 | 79±3 | 80±3 | 80±4 | 80±4 |
| | 62 | 98±5 | 103±6 | 107±4 | 99±4 |
| | 70 | 46±4 | 50±4 | 52±4 | 46±4 |
| total | | 91±55 | 89±36 | 90±40 | 88±41 |
| Male | 22 | 52±3 | 49±3 | 49±2 | 48±2 |
| | 28 | 98±7 | 109±8 | 91±4 | 93±7 |
| | 33 | 29±3 | 33±2 | 32±1 | 30±1 |
| | 37 | 53±3 | 93±3 | 49±4 | 51±4 |
| | 37 | 28±3 | 29±4 | 24±2 | 26±3 |
| | 38 | 62±2 | 63±2 | 54±1 | 52±1 |
| | 55 | 50±8 | 52±8 | 45±4 | 50±2 |
| | 64 | 77±9 | 71±5 | 83±3 | 86±2 |
| | 66 | 36±5 | 33±6 | 37±9 | 36±7 |
| | 68 | 41±4 | 42±3 | 39±5 | 40±5 |
| total | | 53±22 | 57±27 | 50±21 | 51±22 |
| Grand total | | 70±43 | 72±34 | 68±36 | 67±36 |

with the sex difference, the mean colony count of female is relatively larger, but not statistically significant, than male one (91 vs. 53), however ritodrine had no significant effect on colony formation by the female marrows as well as the male ones.

## Discussion

Drug-induced agranulocytosis may be the result of decreased precursor cell proliferation, cell loss in the maturation process, increased margination in the circulation, increased peripheral destruction, or a combination of these mechanisms[1]. However, the pathophysiologic mechanisms of the drug action are pooly understood. Ritodrine hydrochloride is one of the selective $\beta_2$-agonists and the tocolytic effect appears through the stimulation of catecholamine $\beta_2$-receptor. Moreover, most of its side effects, such as tachycardia, palpitation, hyperglycemia and so on, must result from the stimulation of $\beta_1$-and/or $\beta_2$-receptors. Therefore, we examined the direct effect of retodrine on the bone marrow function, especially on the granuloid precursors, using in vitro CFU-GM assay. Applied doses of the drug were determined by the results of our previous investigation in which we measured the serum levels (when mean given dose was 143$\mu$g/min, mean serum level was 103ng/ml) in preterm labor patients under prolonged ritodrine treatment[4]. Consequently, there were no significances between control and ritodrine contained medium in CFU-GM assay. Furthermore, there were not any significances between male and female. The present results suggest that ritodrine has no effect on the granuloid precursors but on their maturation processes. Case report by Ikushima et al.[3] supports our in vitro results. The present CFU-GM assay is very useful to clarify the mechanism of drug-induced agranulocytosis when we will encounter the patient in the future.

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