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Potential Salvage Therapy for Accidental Intrathecal Vincristine Administration: A Preliminary Experimental Study

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Intrathecal vincristine · HOCl · Neurotoxicity · Brain · Rabbits

Abstract
Background: Accidental intrathecal vincristine (VCR) administration results in severe neurotoxicity, usually fatal in outcome. No specific therapy for initrathecal VCR toxicity has been reported so far. In our recent report, complete in vitro degradation of VCR by hypochlorous acid (HOCl) was demonstrated. ***Methods:*** In this comparative study, we examined the in vivo effectivity of HOCl in the cerebrospinal fluid of 24 New Zealand rabbits following intracisternal VCR administration. ***Results:*** There were no significant clinical or histopathologic abnormalities in the control and HOCl groups; however, multiple necrotic foci on histopathological examination of brain sections in the VCR group were determined. There were significantly lower numbers of necrotic foci in brain sections of rabbits which received HOCl administration than those without therapy. ***Conclusion:*** Our results indicate that HOCl may reduce VCR neurotoxicity.

Introduction

Vincristine (VCR) is widely used as a chemotherapeutic agent for the treatment of various malignancies. It is used only via an intravenous route for systemic chemotherapy; in rare instances, it is accidentally administered via an intrathecal route. Intrathecal VCR administration is contraindicated because of fatal neurotoxicity [1–4]. There have been many therapeutic trials for the reduction of

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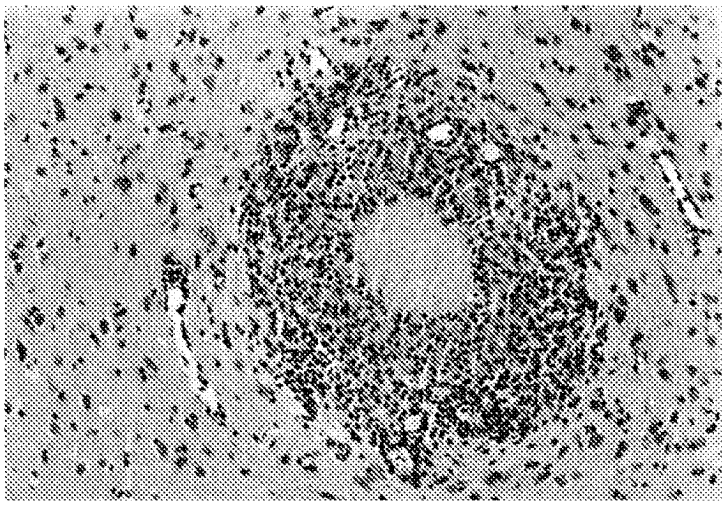

Fig. 1. A necrotic focus in a brain parenchyma. HE. × 50.

intrathecal VCR toxicity, but this is usually ineffective [5–8]. No antidote for VCR has been presented so far, excluding our recent report concerning in vitro degradation of VCR by hypochlorous acid (HOCl) [9]. This study yielded no specific therapy for accidental intrathecal VCR administration. We aimed to reduce the neurotoxic effects of accidentally administered intrathecal VCR using HOCl. In this experimental preliminary study, we investigated the in vivo effectivity of HOCl against intrathecal VCR toxicity in New Zealand rabbits.

Materials and Methods

Chemicals

Vincristine sulfate was purchased from David Bull Laboratories (Mulgrave, Victoria, Australia) and sodium hypochloride (5%) from Fisher Scientific (Pittsburgh, Pa., USA).

Animals

Twenty-four New Zealand rabbits (1,850–2,600 g body weight) were obtained from the Elazığ Animal Research Center.

The rabbits were divided into four groups as follows: control, HOCl, VCR and VCR plus HOCl. We administered 0.5 ml of saline to the control group, 3 μmol/kg HOCl in 0.5 ml of saline to the HOCl group, 0.05 μmol/kg VCR in 0.5 ml of saline to the VCR group and 3 μmol/kg HOCl in 0.25 ml of saline followed 5 min later by 0.05 μmol/kg VCR in 0.25 ml of saline to the VCR plus HOCl group. All medications were given through cisterna magna puncture under ketamine anesthesia.

All animals were observed for extremity paralysis, nystagmus, convulsion, respiration performance and consciousness and were sacrificed following ketamine-xylazine anesthesia on the 4th day. The brains of the rabbits were totally removed and dissected on the sagittal plane. Specimens were fixed in 10% formaldehyde for at least 5 days. After fixation, the specimens were processed in the usual manner and embedded in paraffin. Five-micrometer-thick slides were obtained and stained by the hematoxylin-eosin method. On low-power examination, the total number of necrotic foci of each brain section representing the whole brain on the sagittal plane were counted (fig. 1), then the degree of meningeal and periventricular lymphocytic infiltration was assessed as mild, moderate or severe (fig. 2).

Statistical Analysis

Statistical evaluation was performed using the Mann-Whitney U test.

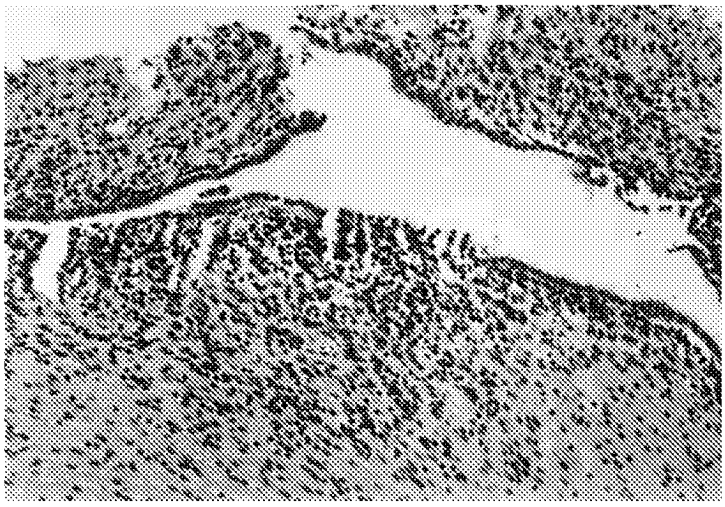

Fig. 2. Dense periventricular lymphocytic infiltration. HE. × 50.

Results

There were no clinical abnormalities in the control and HOCl group after observation for 4 days.

Quadriparesis developed within 18–24 h and progressed to quadriplegia on the 2nd day in all rabbits of the VCR group. Quadriparesis occurred within 36–48 h of VCR administration but did not progress to quadriplegia in the VCR plus HOCl group. While there was only tachypnea in the VCR plus HOCl group, dyspnea and irregular respiration occurred on the 4th day in the VCR group. On the 4th day after VCR administration, all rabbits in the VCR group became comatose, whereas only a lethargic picture was observed in 4 rabbits in the VCR plus HOCl group during the same period (table 1). No nystagmus or convulsive fits were detected in any of the groups.

There was no histopathologic abnormality in brain sections of the control group. Lymphocytic infiltrations in periventricular, perivascular and leptomeningeal areas were detected in other groups. The infiltration was mild, moderate and severe in the HOCl, VCR plus HOCl and VCR groups, respectively. There was a significantly lower number of necrotic foci in brain sections of rabbits in the VCR plus HOCl group compared with the VCR group ($p < 0.01$) (table 2). We could not detect necrotic foci in brain sections of the HOCl group.

Discussion

Accidental intrathecal VCR administration is a life-threatening condition and remains an unsolved problem. Intrathecal VCR administration has been fatal in all reported cases except for 3, in which aggressive treatment was undertaken with CSF replacement; 1 of these, treated with CSF exchange through immediate ventriculostomy, survived without neurologic sequelae [1–5]. Other therapies, such as CSF aspiration by lumbar puncture, administration of glutamic acid, folinic acid, pyridoxine, hydrocortisone and dexamethasone, are empirical [5–8].

Table 1. Clinical findings of the VCR versus VCR plus HOCl group

No.	Group	Lethargy	Coma	Paresis	Plegia	Tachypnea	Irregular respiration
1	VCR	+	+	+	+	+	+
2	VCR	+	+	+	+	+	+
3	VCR	+	+	+	+	+	+
4	VCR	+	+	+	+	+	+
5	VCR	+	+	+	+	+	+
6	VCR	+	+	+	+	+	+
7	VCR+HOCl	+	–	+	–	+	–
8	VCR+HOCl	+	–	+	–	+	–
9	VCR+HOCl	+	–	+	–	+	–
10	VCR+HOCl	+	–	+	–	+	–
11	VCR+HOCl	+	–	+	–	+	–
12	VCR+HOCl	+	–	+	–	+	–

Table 2. Histopathological findings of the VCR versus VCR plus HOCl group

No.	Group	Periventricular infiltration	Perivascular infiltration	Leptomeningeal infiltration	Necrotic foci
1	VCR	+	–	++	3
2	VCR	++	+	+++	6
3	VCR	++	++	++	3
4	VCR	++	+	++	3
5	VCR	+	+	+	9
6	VCR	++	++	++	3
7	VCR+HOCl	+	+	+	0
8	VCR+HOCl	+	+	+	1
9	VCR+HOCl	+	+	+	1
10	VCR+HOCl	+	–	+	0
11	VCR+HOCl	++	+	++	0
12	VCR+HOCl	++	+	+	1

Complete degradation of VCR by HOCl has been reported in our previous study [9]. The mechanism by which HOCl degrades VCR, and dose and time standardization of HOCl for intrathecal VCR toxicity are not known. We used a systemic therapeutic dose of VCR as the intrathecal dose and an HOCl dose according to previous in vitro experiences. These doses of VCR and HOCl may be inappropriate and may have limited effects for the reduction of VCR toxicity. The dose and timing of HOCl administration need further investigation.

Clinical findings of intrathecal VCR administration are headache, extremity paralysis/plegia, loss of deep tendon reflexes, urinary retention, fever, somnolence/lethargy/coma, hearing loss, diplopia, dysphagia, respiratory difficulties, convulsion and nystagmus [2, 3, 5, 6, 10]. We did not perform observations of headache, deep tendon reflexes, hearing loss, urinary retention, fever, diplopia and dysphagia because of technical difficulties. We detected paralysis/plegia, lethargy/coma and respiratory difficulties mainly in the VCR group, in which these findings were more severe than in the VCR plus HOCl group. Our clinical findings indicate that HOCl may inactivate VCR in vivo.

Williams et al. [2] reported that intrathecal VCR administration results in chemical leptomeningitis and focal ventriculitis with underlying necrotizing cerebritis of the brain stem and cerebellar cortex on postmortem histopathological examinations. Our histopathological results are consistent with these findings. Our clinical and histopathological findings in the HOCl group may indicate that HOCl can be used intrathecally for limited indications. Although HOCl cannot prevent clinical abnormalities resulting from VCR toxicity, it reduces the number of necrotic foci and the severity of lymphocytic infiltration in brain samples. This is probably due to the HOCl dose and/or timing. Further experimental studies with different time and dosage modalities are being carried out.

As a conclusion, our preliminary results indicate that HOCl can be used intrathecally or intracisternally for the reduction or prevention of intrathecal VCR toxicity. These preliminary results are not sufficient for the clinical application of HOCl and further preclinical dose-time studies are required before extensive clinical trials are undertaken.

References

1 Michelagnoli MP, Bailey CC, Wilson I, Livingston J, Kinsey SE: Potential salvage therapy for inadvertent intrathecal administration of vincristine. Br J Haematol 1997;99:364–367.

2 Williams ME, Walker AN, Bracikowski JP, Garner L, Wilson KD, Carpenter JT: Ascending myeloencephalopathy due to intrathecal vincristine sulfate. A fatal chemotherapeutic error. Cancer 1983;51:2041–2047.

3 Manelis J, Freundlich E, Ezekiel E, Doron J: Accidental intrathecal vincristine administration. Report of a case. J Neurol 1982;228:209–213.

4 Gaidys WG, Dickerman JD, Walters CL, Young PC: Intrathecal vincristine: Report of a fatal case despite CNS washout. Cancer 1983;52:799–801.

5 Meggs WJ, Hoffman RS: Fatality resulting from intraventricular vincristine administration. J Toxicol Clin Toxicol 1998;36:243–246.

6 Zaragoza MR, Ritchey ML, Walter A: Neurologic consequences of accidental intrathecal vincristine: A case report. Med Pediatr Oncol 1995;24:61–62.

7 Jackson DV, Wells HB, Atkins JN, Zekan PJ, White DR, Richars F, Cruz JM, Musa HB: Amelioration of vincristine neurotoxicity by glutamic acid. Am J Med 1988;84:1016–1022.

8 Dyke RW: Treatment of inadvertent intrathecal injection of vincristine. N Engl J Med 1989;321:1270–1271.

9 Özgen Ü, Savasan S, Stout M, Buck S, Ravindranath Y: Further elucidation of mechanism of resistance to vincristine in myeloid cells: Role of hypochlorous acid in degradation of vincristine by myeloperoxidase. Leukemia 2000;14:47–51.

10 Slyter H, Liwnicz B, Herrick MK, Mason R: Fatal myeloencephalopathy caused y intrathecal vincristine. Neurology 1980;30:867–871.