

Tocolytic Agent For Preterm Labour

Magsent[®] Injection 100 mL

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Background to Development

Magsent[®] Injection 100 mL (hereinafter called "the drug") is an injection product containing 10 g of magnesium sulfate and 10 g of glucose.

Since magnesium sulfate was initially marketed as a name of Magnesol^{®(NOTE)} in Japan in 1946, it has been used mainly in obstetrics as an indication for eclampsia.

Currently, magnesium sulfate is used to prevent and treat eclampsia all over the world, and recently, they are also widely used as a drug for preterm labour in the U.S., etc.

The inhibitory effect of magnesium sulfates on uterine contraction has recently been highlighted in Japan, and also its application to preterm labour is increasingly being expected in clinical practice.

The nationwide survey on drugs used for preterm labour treatment that was reported in 1999¹⁾ and 2005²⁾ suggested that magnesium sulfate had been used in a lot of domestic medical facilities, and clinically, had already been positioned as a drug exhibiting inhibitory effects on uterine contraction.

In response to the clinical demand for indication expansion of magnesium sulfate, Toa Pharmaceutical Co., Ltd. promoted R&D to obtain approval of an additional clinical indication for preterm labour.

We reported the results of our multicenter clinical trial³⁾ and effectiveness study⁴⁾ performed in 2000 and 1998 in Japan, respectively, in patients with preterm labour.

Toa Pharmaceutical Co., Ltd. obtained manufacturing approval for magnesium sulfate as an indication for "the inhibition of uterine contraction in preterm labour" in January 2006, in accordance with the Notification of Off-label Use (Study No. 4, Notification No. 104, Evaluation and Licensing Division, Medical Safety Bureau, Ministry of Health and Welfare, dated on February 1, 1999).⁵⁾

Unlike Magnesol^{®(NOTE)} (glass ampule, 20 mL), the drug is provided with 100 mL plastic bottle containing 10 g of magnesium sulfate and 10 g of glucose. The drug was developed as a large-volume preparation in response to clinical demands and for preventing medical accidents, and was renamed "Magsent[®] Injection 100 mL."

NOTE: Magnesol[®] was renamed "Magnesol[®] Injection 20mL" (Approved in September 2005; NHI drug price listing, December 2005).

Product Characteristics

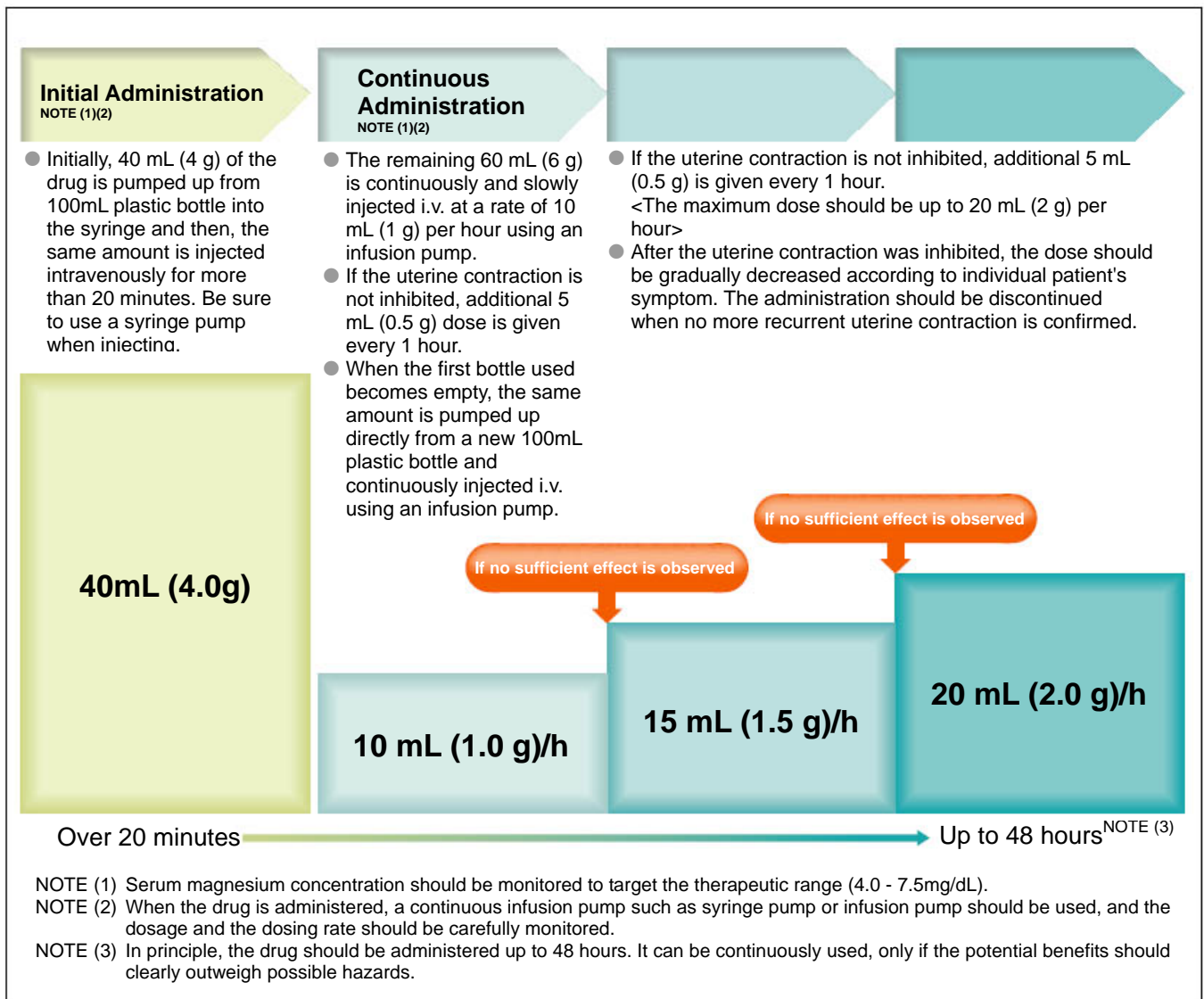
- 1.** The drug is an intravenous injection product containing 10 g of magnesium sulfate and 10 g of glucose in a bottle (100 mL) and is used as a tocolytic agent for preterm labour.
- 2.** The drug inhibited the autokinetic movement of uterus in rats during late-trimester pregnancy (in vitro; rats).
- 3.** In patients with preterm labour, the inhibition rate of uterine contraction (moderate or better improvement) 8 hours after administration of the drug alone was 84.6% (66/78 patients) (in multicenter clinical trial).
- 4.** The drug should be given when the use of ritodrine hydrochloride is limited due to adverse reactions, etc., or when uterine contraction is not inhibited by ritodrine hydrochloride.
NOTE: "Careful administration" should be observed for patients who are receiving ritodrine hydrochloride, and "Precautions for coadministration" should be observed when ritodrine hydrochloride is coadministered (See "Drug Interactions").
- 5.** In clinical trials performed in Japan, 89 (71.8%) out of 124 patients who were evaluated for adverse reaction analysis developed adverse reactions, and the total number of adverse reactions was 197. Among these, known magnesium-induced adverse reactions were mainly included: feeling hot, 64 (51.6%); thirst, 36 (29.0%); flushing, 33 (26.6%); malaise/asthenia, 25 (20.2%), and those which accounted for 80.2% of all adverse reactions observed and mostly occurred on the first day of administration.
The following serious adverse reactions were also observed: magnesium intoxication, cardio-respiratory arrest, respiratory arrest, respiratory failure, rhabdomyolysis, pulmonary oedema and ileus (paralysis intestinal).

Administration Method for Magsent[®] Injection 100 mL

Dosage and Administration

Forty mL of Magsent Injection 100 mL (4 g of magnesium sulfate) is intravenously injected for more than 20 minutes as a loading dose, and subsequently 10 mL (1 g) is continuously administered every 1 hour. If the uterine contraction is not inhibited, additional dose of 5 mL (0.5 g) is given every 1 hour, but the maximum dose should be up to 20 mL (2 g) per hour. After the uterine contraction was inhibited, the dose should be gradually decreased according to individual patient's symptom. The administration should be discontinued when no more recurrent uterine contraction is confirmed.

The drug must be injected using a continuous infusion pump.



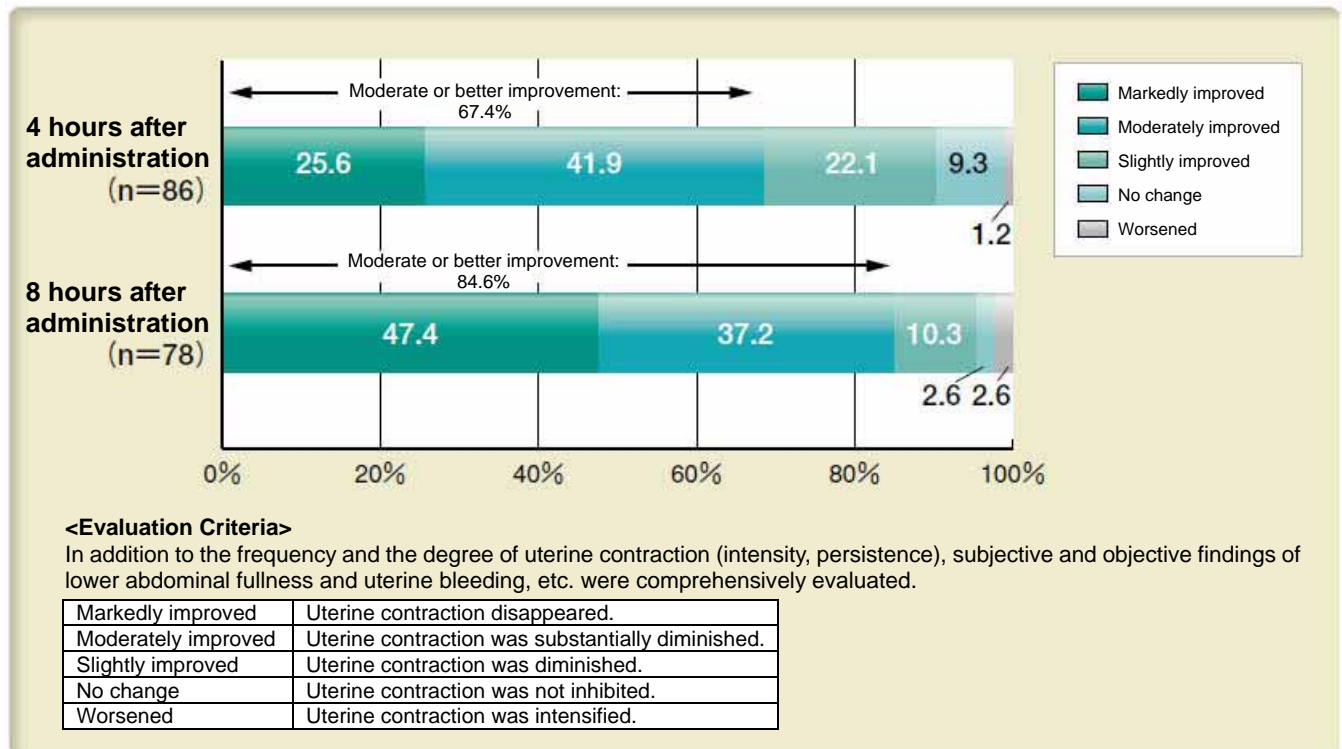
<Precautions for Dosage and Administration>

- The drug must not be used directly from the plastic bottle as initial dose. When the drug is used as initial dose, 40 mL of the drug (4 g of magnesium sulfate) should be pumped up from the bottle into the syringe. The remaining 60 mL should be continuously injected i.v. using an infusion pump.
- In principle, the drug should be administered up to 48 hours. It can be continuously used, only if the potential benefits should clearly outweigh possible hazards, and should not be administered irresponsibly.
- Blood magnesium concentration should be monitored during administration with careful attention to avoid adverse reactions.
- Careful observation is required to prevent possible magnesium intoxication during administration.
 - Patellar reflex test, checking a change in breathing frequency and urine volume measurement performed before administration and after dose increase.

Clinical Trial Results [1] <Multicenter Clinical Trial>

[Primary Effect] Inhibitory effect on uterine contraction

Administration of the drug alone showed a moderate or better improvement in the inhibition of uterine contraction 4 and 8 hours after administration: 67.4% (58/86 patients) and 84.6% (66/78 patients), respectively.*



Subject: 103 patients with preterm labour

■ Inclusion Criteria

(1) Patient at after 22 weeks and 0 day to before 37 weeks and 0 day of gestation. (2) Patient whose uterine is subjectively or objectively contracted at least 4 times per hour and the contraction persists for at least 20 seconds. (3) Patient whose cervical dilation is less than 3 cm in size, and the rate of cervical effacement is less than 80%.

■ Exclusion Criteria

(1) Patient whose membranes ruptured (2) Patient with a history of myasthenia gravis or heart block, and patient with hypotonic dehydration (3) Patient with renal disorder (4) Patient with intrauterine infection (5) Fetal malformation, fetal infection, fetal distress or fetal death (6) Patient developed premature separation of normally implanted placenta (7) Patient younger than 20 years of age (8) Other patients who were excluded by physicians' judgment

Administration Method:

Forty mL of the drug (4 g of magnesium sulfate) is intravenously injected for more than 20 minutes as a loading dose, and subsequently 10 mL (1 g) is continuously administered i.v. every 1 hour. If the uterine contraction is not inhibited, additional dose of 5 mL (0.5 g) is given every 1 hour, but the maximum dose should be up to 30 mL (3 g) per hour. After the uterine contraction was inhibited, the dose should be gradually decreased according to individual patient's symptom. The administration should be discontinued when no more recurrent uterine contraction is confirmed.

Adverse Reaction:

Of 94 patients, 72 (76.6%) developed 10 adverse reactions, with 10 abnormal laboratory test results. Among these, known magnesium-induced adverse reactions were mainly included: feeling hot, 50 (53.2%); thirst, 34 (36.2%); flushing, 26 (27.7%); malaise/asthenia, 21 (22.3%), and those which accounted for 80.4% of all adverse reactions and mostly occurred on the first day of administration and tended to disappear within 3 days after administration.

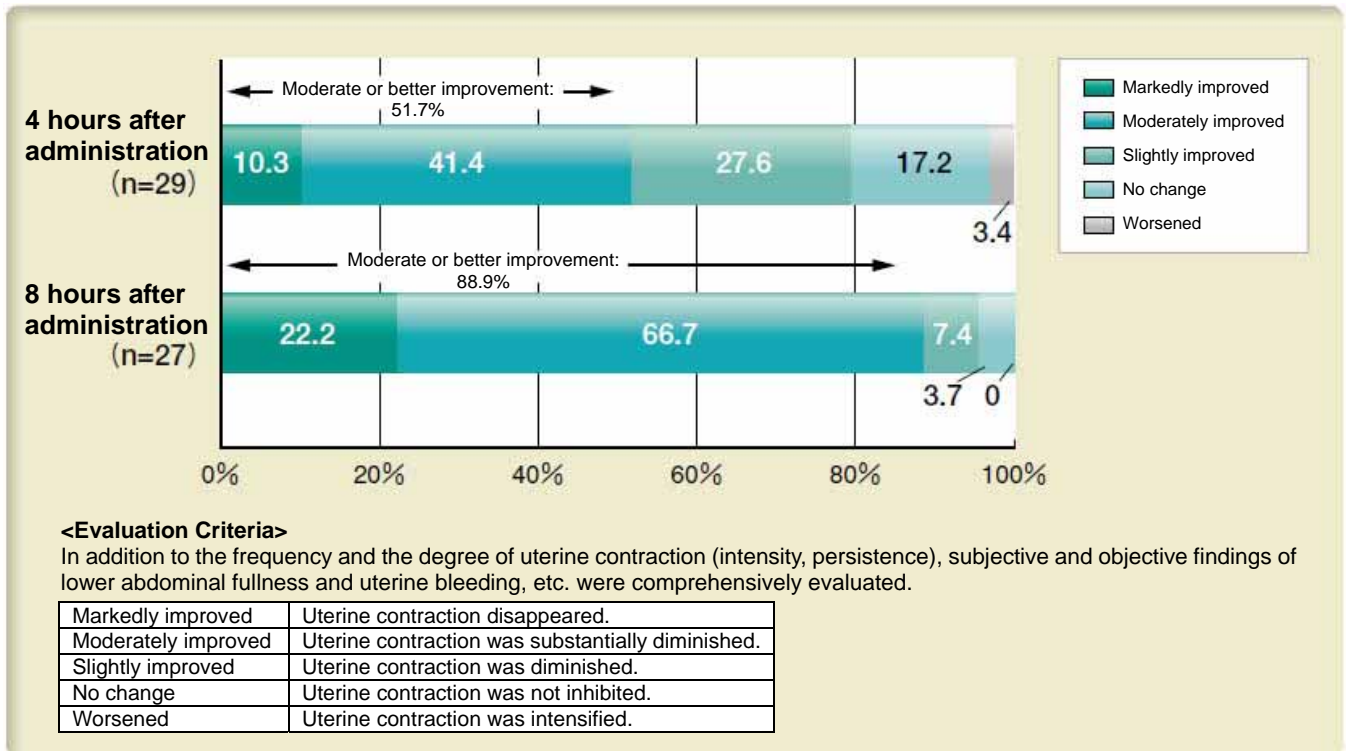
Sato, K., et. al.: Sanka-to-fujinka in Japanese; 67(1), 122-139, 2000; partly revised*

* In this booklet, patients were reanalyzed according to the approved dosage and administration.

Clinical Trial Results [2] <Effectiveness Study>

[Primary Effect] Inhibition of Uterine Contraction

Administration of the drug alone showed a moderate or better improvement in the inhibition of uterine contraction 4 and 8 hours after administration: 51.7% (15/29 patients) and 88.9% (24/27 patients), respectively.



Subject: 32 patients with preterm labour

■ **Inclusion Criteria**

(1) Patient at after 22 weeks and 0 day to before 37 weeks and 0 day of gestation. (2) Patient whose uterine is subjectively or objectively contracted at least 4 times per hour and the contraction persists for at least 30 seconds. (3) Patient whose uterine contraction cannot be inhibited at the maximum dose of ritodrine hydrochloride (200 µg/min) (4) Patient who ritodrine hydrochloride administration was discontinued or the dosage cannot be increased due to adverse reactions. (5) Patient whom the use of ritodrine hydrochloride is inappropriate, due to hyperthyroidism, toxemia of pregnancy or other symptom.

■ **Exclusion Criteria**

(1) Patient with a history of myasthenia gravis or heart block, and patient with hypotonic dehydration (2) Patient with renal disorder (3) Patient with intrauterine infection (4) Fetal infection, fetal distress or fetal death (5) Patient developed premature separation of normally implanted placenta (6) Other patients who were excluded by physicians' judgment

Administration Method:

The drug was administered alone or in combination of other drugs.

■ **Administration of the drug alone**

In principle, 4 g of magnesium sulfate was slowly injected i.v. for more than 20 minutes, and subsequently the same dose was maintained at a rate of 1 g per hour. The dosage was increased or decreased according to the patient's symptom.

■ **Combined Administration**

When ritodrine hydrochloride was concomitantly used, magnesium sulfate dose was maintained constant and ritodrine hydrochloride dose was decreased to its initial dose. Afterward, the dose was titrated according to the patient's symptom.

Administration period was set up to 36 weeks and 6 days of gestation. If no inhibitory effect on uterine contraction was observed and patients' symptoms were worsened during this period, or if continuous administration was considered inappropriate due to adverse reactions, changing to other more adequate treatment was to be permitted.

Adverse Reaction:

Of 30 patients, 17 (56.7%) developed adverse reactions (totally 32 adverse reactions). These adverse reactions included feeling hot, 13 (43.3%); and flushing, 7 (23.3%). Most symptoms were mild and the patients could continuously receive administration. Only 1 patient discontinued administration due to respiratory distress.

Kawarabayashi T., et al.: Sanka-to-fujinka in Japanes; 65(4), 535-541, 1998

"Precautions for Indications"

2) The drug should be administered when the use of ritodrine hydrochloride is limited due to adverse reactions, or when uterine contraction is not inhibited by ritodrine hydrochloride.

"Dosage and Administration"

Forty mL of the drug (magnesium sulfate 4 g) is intravenously injected for more than 20 minutes as a loading dose, and subsequently 10 mL (1 g) is continuously administered every 1 hour. If the uterine contraction is not inhibited, additional dose of 5 mL (0.5 g) is given every 1 hour, but the maximum dose should be up to 20 mL (2 g). After the uterine contraction was inhibited, the dose should be gradually decreased according to individual patient's symptom. The administration should be discontinued when no more recurrent uterine contraction is confirmed. The drug should be injected using a continuous infusion pump. NOTE: "Careful administration" should be observed for patients who receive ritodrine hydrochloride, and "Precautions for coadministration" should be observed when ritodrine hydrochloride is coadministered (See "Drug Interactions").

Adverse Reaction

In clinical trials performed in Japan, 89 (71.8%) out of 124 patients who were analyzed for safety evaluation developed adverse reactions, and the total number of reactions was 197. Among these, known magnesium-induced adverse reactions were mainly included: feeling hot, 64 (51.6%); thirst, 36 (29.0%); flushing, 33 (26.6%); malaise/asthenia, 25 (20.2%), which accounted for 80.2% of all adverse reactions observed and mostly occurred on the first day of administration.

Incidence of Adverse Reactions

Category of Study		Multicenter Clinical Trial	Effectiveness Study	Total
Number of subjects who were analyzed for safety evaluation		94	30	124
Number of subjects who developed adverse reactions (%)		72 (76.6)	17 (56.7)	89 (71.8)
Incidence of adverse reactions (number)		165	32	197
Category of Disease	Name of adverse reactions	Incidence of adverse		
Hematological	Epistaxis	1 (1.1)	0 (0.0)	1 (0.8)
Respiratory	Dyspnoea	4 (4.3)	2 (6.7)	6 (4.8)
Cardiovascular	Flushing	26 (27.7)	7 (23.3)	33 (26.6)
	Palpitations	1 (1.1)	0 (0.0)	1 (0.8)
	Arrhythmia	1 (1.1)	0 (0.0)	1 (0.8)
Gastroenterological	Paralysis intestinal	1 (1.1)	0 (0.0)	1 (0.8)
	Thirst	34 (36.2)	2 (6.7)	36 (29.0)
	Nausea	5 (5.3)	1 (3.3)	6 (4.8)
	Vomiting	4 (4.3)	1 (3.3)	5 (4.0)
	Anorexia	2 (2.1)	2 (6.7)	4 (3.2)
	Diarrhoea	1 (1.1)	0 (0.0)	1 (0.8)
Psychoneurotic	Feeling hot	51 (54.3)	13 (43.3)	64 (51.6)
	Malaise	11 (11.7)	4 (13.3)	15 (12.1)
	Asthenia	10 (10.6)	0 (0.0)	10 (8.1)
	Headache	5 (5.3)	0 (0.0)	5 (4.0)
	Abnormal visual acuity	2 (2.1)	0 (0.0)	2 (1.6)
	Accommodation disorder	2 (2.1)	0 (0.0)	2 (1.6)
	Diplopia	1 (1.1)	0 (0.0)	1 (0.8)
	Diminished reflexes	1 (1.1)	0 (0.0)	1 (0.8)
	Diminished perception	1 (1.1)	0 (0.0)	1 (0.8)
Injected Site	Vascular pain	1 (1.1)	0 (0.0)	1 (0.8)

(Values when approved in January 2006)

List of Abnormal Laboratory Test Results

Category of Study		Multicenter Clinical Trial	Effectiveness Study	Total
Number of subjects who were analyzed for safety evaluation		94	30	124
Number of subjects indicating abnormal laboratory test results (%)		8 (8.5)	1 (3.3)	9 (7.3)
Number of abnormal laboratory test results		10	2	12
Laboratory test results Abnormal test values/ Incidence (%)	Elevated phosphorus	2 (2.1)	0 (0.0)	2 (0.6)
	Elevated AST (GOT)	2 (2.1)	1 (3.3)	3 (2.4)
	Elevated ALT (GPT)	2 (2.1)	1 (3.3)	3 (2.4)
	Elevated total cholesterol	3 (3.2)	0 (0.0)	3 (2.4)
	Elevated blood glucose	1 (1.1)	0 (0.0)	1 (0.8)

(Values when approved in January 2006)

■ Reference: Serum Magnesium Concentration and Toxic Symptoms

Monitoring of serum magnesium concentration is important for safe use of magnesium sulfate. Administration method and dosage should be carefully noted to maintain the therapeutic drug concentration range of 4 - 7.5 mg/dL. For dose adjustment, patellar reflex, breathing frequency and urine volume should also be carefully noted.

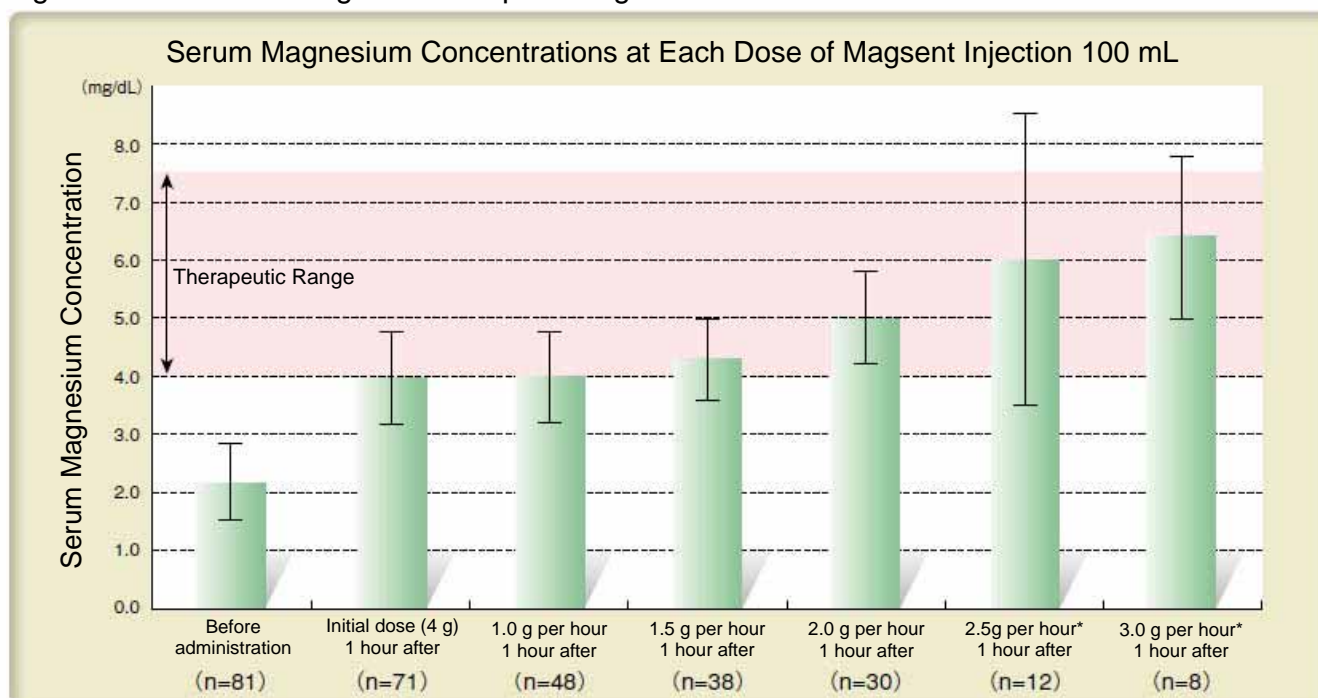
In the case of overdose administration, hypermagnesemia may occur in mothers and newborns and the following symptoms may be observed: feeling hot, flushing, thirst, decreased blood pressure, CNS depression, depressed cardiac function, respiratory paralysis and skeletal muscle relaxation.^{1,2)} Calcium preparations are reportedly effective for treatment.^{3,4)} A correlation between serum magnesium concentration and toxic symptoms shown in the table below is well known.⁵⁻¹¹⁾

Concentration (mg/dL)	Symptom
4 - 7.5	Therapeutic range
8.4 - 12	Patellar tendon reflex absent
12 - 14.4	Respiratory depression
Higher than 14.4	Respiratory paralysis, Respiratory arrest Arrhythmia (atrioventricular block, conduction disorder)

- 1) McCubbin, J. H., et al.: Lancet, 1, 1058, 1981.
- 2) Wax, J.R., et al.: J. Gynecol. Obstet., 48, 213-214, 1995.
- 3) Fukushima, M. (editorial supervisor): Preeclampsia and Eclampsia; Japanese edition of The Merck Manual of Diagnosis and Therapy 17th Edition, 2061-2062, Nikkei BP, 1999.
- 4) Cao, T. Z., et al.: Clin. Chim. Acta, 285, 191-193, 1999.
- 5) Sato, K., et al.: **Sanka-to-fujinka in Japanes**, 67, 122-139, 2000.
- 6) American Society of Health-System Pharmacists, Inc.: Magnesium Sulfate, AHFS DRUG INFORMAT10N 2004, 2142-2145
- 7) Ramsey, P. S., Rouse, D. J.: Semin Perinatol. 25(4), 236-247, 2001.
- 8) Winkler, A. W., et al.: J. Clin. Invest. 21, 207-216, 1942.
- 9) Medical Economics: Magnesium Sulfate, Injectable, in PDR Generics. 4th ed. Montvale NJ, 1777-1778, 1998.
- 10) Ohshige, T., et al.: ICU-to-CCU in Japanese, 20(5), 365-373, 1996.
- 11) Hollander, D. I., et al.: Am. J. Obstet. Gynecol., 156(3), 631-637, 1987.

Magsent[®] Injection 100 mL and Serum Magnesium Concentration

Measurements of serum magnesium concentrations at 4 g as a loading dose and 1.0 - 3.0 g per hour as maintaining dose revealed that therapeutic drug concentration range was "4.0 - 7.5 mg/dL" at the maintaining doses of up to 2.0 g/h.



Time of Measurement		n	Serum Magnesium Concentration (mg/dL)	
			(Mean ± SD)	Minimum to Maximum (Median Value)
Before administration		81	2.2±0.7	1.3~5.0 (2.0)
Initial Dose 40 mL (4 g) 1 hour after administration		71	4.0±0.8	1.6~6.0 (3.9)
Maintaining Dose	10 mL (1.0 g) per hour 1 hour after administration	48	4.0±0.8	2.4~6.6 (3.8)
	15 mL (1.5 g) per hour 1 hour after administration	38	4.3±0.7	2.4~5.7 (4.3)
	20 mL (2.0 g) per hour 1 hour after administration	30	5.0±0.8	3.2~7.0 (5.1)
	25 mL (2.5 g) per hour* 1 hour after administration	12	6.0±2.5	3.9~13.4 (5.45)
	30 mL (3.0 g) per hour* 1 hour after administration	8	6.4±1.4	4.8~9.5 (6.1)

* Because there were cases that serum magnesium concentration exceeded the therapeutic range at more than 25 mL (2.5g) doses per hour and reached the toxic range, the approved dosage and administration were determined to be up to 20 mL (2 g) per hour.

Subject:

Patients with preterm labour at after 22 weeks and 0 day to before 37 weeks and 0 day of gestation, whose uterine is contracted at least 4 times per hour and the contraction persists for at least 20 seconds, with cervical dilation less than 3 cm in size and the rate of cervical effacement less than 80% (multicenter clinical trial).

Administration Method:

Forty mL of the drug (4 g of magnesium sulfate) is intravenously injected for more than 20 minutes as initial dose, and subsequently 10 mL (1 g) is continuously administered i.v. every 1 hour. If no sufficient effect was observed, the dosage was increased to 15 mL (1.5 g), 20 mL (2 g) and 30 mL (3 g) at maximum.

Measurement Method:

Serum magnesium concentration was measured at each doses of the drug 1 hour after administration.

Sato, K., et al.: Sanka-to-fujinka in Japanese, 67, 122-139, 2000

"Dosage and Administration"

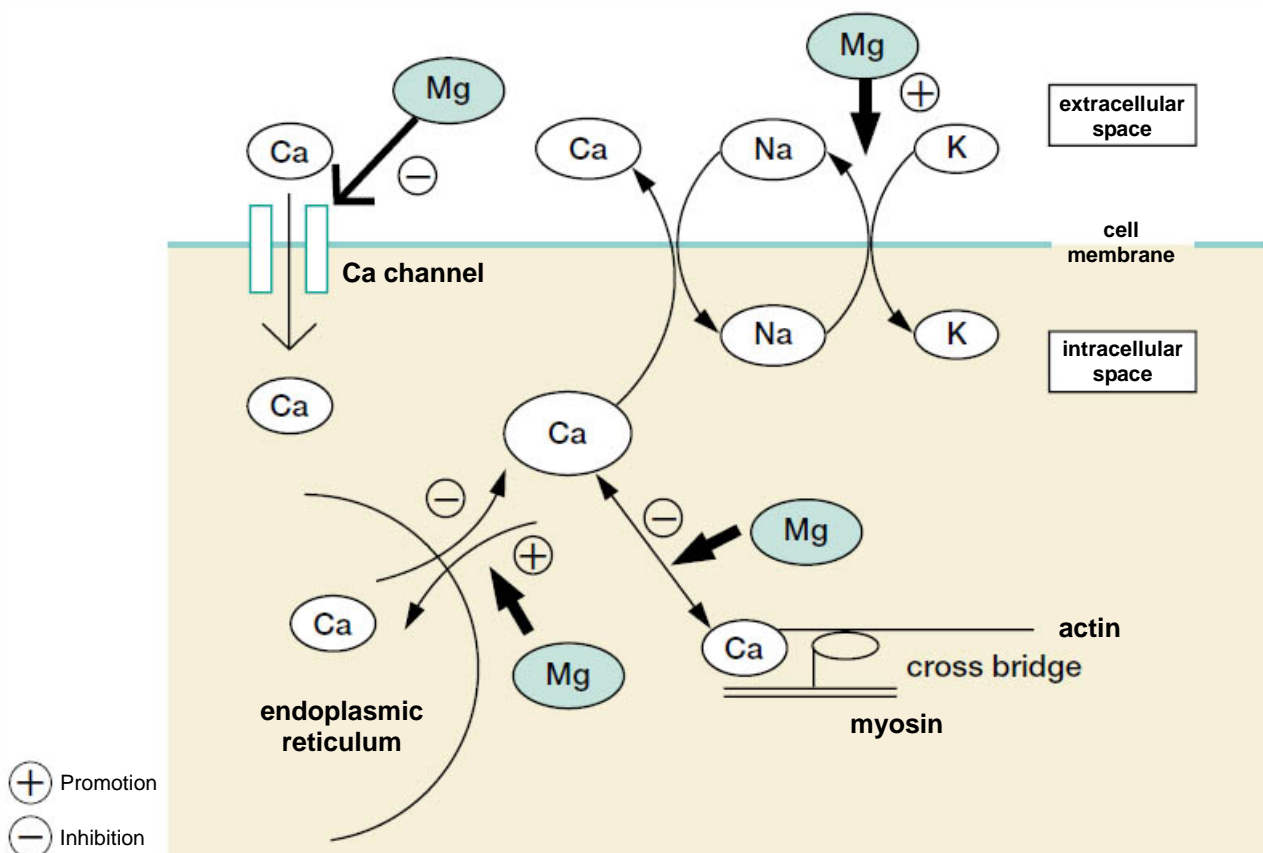
Forty mL of the drug (4 g of magnesium sulfate) is intravenously injected for more than 20 minutes as a loading dose, and subsequently 10 mL (1 g) is continuously administered every 1 hour. If the uterine contraction is not inhibited, additional dose of 5 mL (0.5 g) is given every 1 hour, but the maximum dose should be up to 20 mL (2 g) per hour. After the uterine contraction was inhibited, the dose should be gradually decreased according to the patient's symptom. The administration should be discontinued when no more recurrent uterine contraction is confirmed. The drug must be injected using a continuous infusion pump.

Mechanism of Action

The mechanism of action of magnesium is as follows:¹⁻⁵⁾

- (1) Calcium channels are blocked to inhibit the calcium influx from the extracellular space into cells.
- (2) Na^+ , K^+ -ATPase and Ca^{2+} -ATPase are activated to promote the flow of calcium from inside to outside the cells.
- (3) Phospholipase C activity specific for inositol trisphosphate (IP_3) is inhibited not to produce IP_3 and to block IP_3 -induced calcium release from intracellular calcium storage sites (endoplasmic reticulum).
- (4) Ca^{2+} -ATPase is activated to promote the uptake of calcium into the endoplasmic reticulum within cells.
- (5) A decrease in intracellular free calcium leads to the inactivation of calmodulin-mediated myosin light chain kinase, thereby inhibiting muscle contraction induced by actin-myosin sliding.

Mechanism of Action



- 1) Matsumoto, T., et al.: Sunfujinka No Jitsusai. 40(2), 163-172, 1991.
- 2) Asokan, K. T., et al.: Eur. J. Pharmacol. 455, 65-71, 2002.
- 3) Fawcett, W. J., et al.: Br. J. Anesthesia. 83(2), 302-320, 1999.
- 4) Hurd, W. W., et al.: Am. J. Obstet. Gynecol. 187(2), 419-424, 2002.
- 5) Miyoshi, H. and Ohama, K.: Sanfujinka-no-sekai in Japanese, 55(7), 765-772, 2003.