Mazaticol for Treating Parkinson

Yoshiki Niimi and Tatsuro Mutoh

Contents

Abstract

Mazaticol, 6,6,9-trimethyl-9-azabicyclo[3,3,1]non-3β-yl-α,α-di-(2-thienyl) glycolate hydrochloride monohydrate, was developed by Tanabe Seiyaku Co. LTD. in1970s and started selling in 1978 in Japan. This agent has an anticholinergic activity in the central nervous system as the same degree of well-known anticholinergic medicine, trihexyphenidyl. Mazaticol and other anticholinergic agents are considered to block the muscarinic acetylcholine receptors and cholinergic nerve activity. Mazaticol has an affinity to M1 and M2 muscarinic acetylcholine receptor and had less peripheral

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activity compared to other anticholinergic agents. In the animal experiments, mazaticol exhibited inhibitory effects on dopamine uptake in the striatal nerve terminal. As for clinical indication, mazaticol is applied mainly to a psychotropic drug-induced parkinsonian syndrome. Many clinical evaluations showed efficacy of mazaticol is almost as same as the other anticholinergic agents. But mazaticol showed the improvement of symptoms for the cases in which other drugs had no effects. However, current clinical studies on mazaticol are not enough, especially for the idiopathic parkinsonian disease.

Chemistry, Developmental History

Development History

It was not until the late 1960s when levodopa treatment for Parkinson's disease had begun to establish. At that time, many drugs such as belladonna alkaloids, antihistamines, synthetic alkaloids, benztropine, phenothiazine, dextroamphetamine, etc. had been used to treat parkinsonian patients. However, greater part of these agents was no means satisfactory to be effective for the symptoms of parkinsonian syndrome. For example, belladonna alkaloids required a large amount of dosage to be effective, consequently, it tended to cause unwanted side effects such as intraocular pressure elevation, dysuria, and dyspnea. Consequently, antihistamines or synthetic alkaloids were commonly used. Still the former exhibited mild and insufficient effects, the anticholinergic medicine took an important role in treating parkinsonisms including Parkinson's disease in those days. Unfortunately, anticholinergic agents had also some significant adverse effects such as a dry mouth, mydriasis, and gastric immotility.

The biochemical research laboratory, Tanabe Seiyaku Co., LTD., had been investigating the series of galantamine derivatives because those had strong anticholinergic effects in the central nervous system. Subsequently, Nose et al. found that the 6,6,9-trimethyl-9-azabicyclo[3,3,1]non-3β-yl-α,α-di-(2-thienyl) glycolate hydrochloride monohydrate (mazaticol) had a potency of low side effect and same pharmacological activity against existing anticholinergic agents (Nose et al. 1971). In April 1976, mazaticol acquired the marketing approval as a pharmaceutical product. In March 1978, this drug started selling in Japan for the treatment of psychotropic drug-induced parkinsonism.

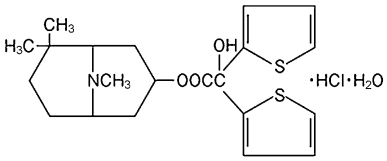
Chemical Characteristics (Pharmaceutical Products Interview form in Japan 2015)

- Mazaticol suppresses the transmission of over extricated acetylcholine.
- Mazaticol has a high affinity to the M2 acetylcholine receptor.

- Anticholinergic effect of mazaticol is rather stronger than trihexyphenidyl in central nervous system but is less than half in the periphery.
- Inhibitory effect against haloperidol-induced catalepsy of mazaticol was as same as trihexyphenidyl.
- The result of clinical trials of mazaticol for psychotropic drug-induced parkinsonism showed the improvement of parkinsonisms.
- Mazaticol showed the improvement of symptom for the cases in which other drugs had no effects.
- The number of reported side effects of mazaticol was 296 out of 3852 (7.7%).

Chemical Formula

6,6,9-trimethyl-9-azabicyclo[3,3,1]non-3β-yl-α,α-di-(2-thienyl) glycolate hydrochloride monohydrate.



Molecular weight: 460.05
CAS registry number:
65,104–02-1 [Mazaticol Hydrochloride Hydrate]
32,891–29-5 [Mazaticol Hydrochloride]
42,024–98-6 [Mazaticol]

Pharmacology

Pharmacokinetics

Metabolism

In rats, only less than 0.1% of orally administered mazaticol discharged unchanged in the urine in 24 h. First, a part of mazaticol was N-demethylated and then hydrolyzed, and the bulk of remainder was hydrolyzed to granatane base and α, α-di(2-thienyl) glycolic acid (DTGA) directly. Furthermore, a part of granatane base was metabolized by glucuronic acid conjugation, and the major metabolites of granatane base were 6,6,9-trimethyl-3-hydroxy-granatane, 6,6-dimethyl-3-hydroxygranatane, and their glucuronic acid conjugates. Most of DTGA was metabolized by dethienylation, decarboxylation, glucuronic acid conjugation, and mercapturic acid conjugation, and the major metabolites of DTGA were glucuronic acid conjugate of DTGA, glucuronic acid conjugate of 2-thiophenecarboxylic acid, N-acetyl-S-[5-(2-thiophenecarbonyl)-2-thienyl]-L-cystine, and 2-thiopheneglyoxylic acid (Meshi et al. 1972).

Excretion

In rats, excretion of orally administered ^{14}C-labelled mazaticol was about 25% in urine, 8% in feces, and 37% in the expired air within 24 h, and about 23% in bile within 6 h. While the excretion rate of intravenously administered mazaticol was 41% in urine, 8% in feces, and 30% in the expired air during 24 h, and 26% in bile within 6 h.

In beagles, 60% of orally administered mazaticol discharged in the urine in 24 h (Otsuka et al. 1972).

Time to Peak

In rats, orally administered mazaticol reached a maximum peak in plasma at 30 min. The time course of absorption curve demonstrated two peaks, a rapid phase with a half-life of 5.8 min and a slow phase with that of 138 min.

In beagles, serum mazaticol concentration was peaked in 3–5 h after oral administration and decreased gradually (Otsuka et al. 1972)

Half-Life Elimination

No data available.

Distribution

In mouse, orally administered ^{14}C-labelled mazaticol showed the radioactivity was concentrated in the brain, liver, intestine, lung, Harder's gland, salivary gland, and kidney. While intravenously administered mazaticol showed high radioactivity in brown fat, salivary gland, Harder's gland, and adrenal cortex.

Blood-Brain Barrier Permeability

No data is available; however, in rats, orally administrated ^{14}C-labelled mazaticol reached a maximum level in the brain in 30–60 min. Concentration in the brain was 27% to 117% compared to that of plasma in 24 h (Otsuka et al. 1972).

Mechanism of Action

Mazaticol and other anticholinergic antiparkinsonian agents are considered to block the muscarinic acetylcholine receptors and cholinergic nerve activity in central and peripheral nervous systems. Relative cholinergic excess compared to dopaminergic activity in the striatum are thought to result in some parkinsonian symptoms such as tremor, bradykinesia, and rigid muscles. Thus, suppression of the effects of acetylcholine gives balances between acetylcholine and dopamine and alleviate parkinsonian syndromes. Also, mazaticol showed the dissociation between central and peripheral anticholinergic activity. Mazaticol had less peripheral activity compared to other anticholinergic agents such as trihexyphenidyl (Nose et al. 1971), (Pharmaceutical products interview form in Japan 2015). Anticholinergic antiparkinsonian drugs have been widely used for the treatment of extrapyramidal disorders for a long time although their pharmacological characterization has been unclear. Katayama et al. studied the rank of potency of the effects of anticholinergic antiparkinsonian

drugs to binding of 3H-QNB and 3H-PZ and calculated the affinity of each drug to the M1 receptor. All drugs were potent inhibitors of 3H-QNB and 3H-PZ binding. The order of potency for 3H-QNB being: mazaticol > atropine > piroheptine > trihexyphenidyl > biperiden > ethopropazine > pirenzepine. The order of potency for 3H-PZ being: mazaticol > atropine > trihexyphenidyl > biperiden > ethopropazine > pirenzepine. Ki ratio indicated that trihexiphenidyl and biperiden bound to the M1 receptors selectively with high affinity, and mazaticol would bind to the M2 receptor with higher affinity than atropine. These data also suggest that mazaticol has the most powerful binding potency to M1 and M2 receptors (Katayama et al. 1990). Though M2 receptor is well-known subtype in smooth muscle and heart, Gomezas et al. showed, M2 receptor plays a key role in mediating muscarinic receptor-dependent movement control. They had generated the mice lacking functional M2 receptor. Injection of increasing doses of the centrally acting, nonselective muscarinic agonist oxotremorine (OXO (0.01–0.3 mg/kg)) into wild-type control mice reproducibly resulted in massive whole-body tremor and akinesia at the highest dose tested (0.3 mg/kg; doses >0.3 mg/kg resulted in a pronounced increase in lethality). Strikingly, the tremorogenic effects of OXO were absent in $M2^{-/-}$ mutant mice, even when the OXO dose was increased. Interestingly, heterozygous $M2^{+/-}$ mutant mice also did not display the OXO-induced tremor response (Gomeza et al. 1999).

Based on the results of randomized controlled trials in Japan and consensus by psychopharmacological experts, Inada et al. determined the dose equivalence of antiparkinsonian drugs. The list includes amantadine, benztropine, biperiden, diphenhydramine, hydroxyzine, mazaticol, metixene, piroheptine, profenamine, promethazine, and trihexyphenidy. The number of dose equivalence is 100, 1, 2, 30, 65, 8, 10, 4, 100, 50, and 4, respectively (Inada and Inagaki 2015).

Anti-acetylcholine Activity

In the experiment on the isolated guinea-pig ileum, mazaticol showed the inhibitory activity against acetylcholine-induced ileum contraction. It was as same as trihexyphenidyl or atropine but was almost half of benztropine. ED_{50} of mazaticol, trihexyphenidyl, atropine, and benztropine was 6.4×10^{-9}, 8.0×10^{-9}, 3.4×10^{-9}, 6.0×10^{-9}, g/ml, respectively.

Anti-Tremorine-Induced Tremor Activity

ED_{50} of orally administrated mazaticol in the mouse was nearly equivalent to that of trihexyphenidyl or atropine (6.2, 7.1, 4.1 mg/kg respectively). But it was almost a quarter of benztropine (1.6 mg/kg).

Anti-Physostigmine-Induced Death Activity

ED_{50} of orally administrated mazaticol against physostigmine-induced death activity in the mouse was rather strong than that of trihexyphenidyl (14.1, 21.4 mg/kg, respectively). But it was almost a half of atropine and one-eighth of benztropine (8.1, and 1.8 mg/kg, respectively).

Effect on Haloperidol-Induced Parkinsonism

In monkeys, orally administrated mazaticol at the doses of 10 and 5 mg/kg suppressed the haloperidol-induced extrapyramidal symptom as the same degree as trihexyphenidyl. Yukawa et al. retrospectively reported that mazaticol did not affect the haloperidol clearance in 218 patients with psychiatric disorders (Yukawa et al. 2002).

Activity to a Dopaminergic Neuron

Mazaticol inhibited dopamine uptake in striatal nerve terminal at the concentration of 10^{-5} mol/L in a rat brain.

Mydriatic Activity

A mydriatic activity of mazaticol was weaker than that of trihexyphenidyl, benztropine, and atropine. ED_{50} of orally administrated each drug to dilate pupils in the mouse was 31, 15, 1.8, and 1.3 mg/kg, respectively.

Anti-Pilocarpine-Induced Salivation Activity

Mazaticol inhibited pilocarpine-induced salivation as the same degree as trihexyphenidyl, but this activity was rather weak than other anticholinergic drugs. ED_{50} of orally administrated each drug (mazaticol, trihexyphenidyl, benztropine, and atropine) to cause salivation in the pilocarpine-prescribed mouse was 9.2, 8.1, 1.2, and 1.9 mg/kg, respectively.

Effects on Gastric Motility in Cats and on Ileum Motility in Rabbits

Mazaticol showed weak suppression to each motility equally to or smaller than that of trihexyphenidyl or atropine.

Indications (of Marketed Products)

Psychotropic drug-induced parkinsonian syndrome. (Pharmaceutical products interview form in Japan 2015).

Clinical Studies

As mazaticol is available only in Japan and its indication is limited to psychotropic drug-induced parkinsonism, clinical studies tended to limit the field of the drug induced parkinsonism of patients with psychotic disorders. Most of the participants of two RCT studies were patients with schizophrenia or other psychotic disorders. Those studies indicate the efficacy of mazaticol for treating the drug-induced parkinsonism. Clinical studies are not enough especially for idiopathic Parkinson's disease or other primary neurodegenerative diseases (Table 1).

Table 1 Surveys review

Study (RCT, Meta-Analysis, NIS; Name/ Acronym, Authors, Year	N, Patients Country/ ies	Study arms, comparators, Placebo	Results (Scores, Response-/ Remissionsrates)	Dropout rates	Relevant and severe side effects
Clinical evaluation, Kosaka, 1971	17 Japan	One-arm No comparator No placebo	Tremor was improved in 14 patients.	2/17	Nausea, dizziness, dull headache
Clinical evaluation, Tanaka (1972)	30 Japan	One-arm No comparator No placebo	80% of subjects showed improvement.	0/30	None
Double-Blind Crossover clinical evaluation, Yagi (1973)	40 Japan	Multicenter double-blind crossover design, trihexyphenidyl, drometazine No placebo	No significant difference in the improvement rate among three agents.	4/40	None
RCT, Fujimura (1976)	12 Japan	Single center double-blind crossover design, amantadine, no placebo	No significant difference between mazaticol and amantadine	0/12	None
RCT, Takesada et al. (1977)	68 Japan	Multicenter double-blind crossover design, amantadine, placebo used	No significant difference between mazaticol and amantadine	3/68	None
Clinical evaluation, Nakajima and Matsuda (1986)	19 Japan	One-arm No comparator No placebo	89.5% of subjects showed improvement	0/19	None

- Kosaka reported the effect of mazaticol for 14 patients with idiopathic parkinsonism, two patients with head tremor and one patient with postural tremor. The dosage of mazaticol was 6 mg or 15 mg per day. Inclusion criteria of parkinsonism were a patient with apparent tremor, rigidity, and akinesia. For 11 of parkinsonism patients and three other tremor patients, mazaticol brought improvement of tremor. Three parkinsonism patients showed improvement in all symptoms. Three patients with parkinsonism showed no response to this medicine. Two patients with parkinsonism could not continue the trial due to nausea, dizziness, and dull headache (Kosaka 1971).
- Tanaka et al. evaluated the efficacy of mazaticol for 30 anti-psychotropic drug induced extrapyramidal symptoms. The dosage of mazaticol was 30 mg, 45 mg, or 60 mg per day. Extrapyramidal symptoms included parkinsonism, akathisia, and dyskinesia. All 30 subjects showed improvement of tremor. Thirteen patients

out of 16 who exhibited muscle rigidity and 13 out of 26 patients with hypokinesia showed improvement. Fifteen out of the 18 patients with akathisia exhibited alleviation. All six patients who showed dyskinesia exhibited the outstanding efficacy. No remarkable side effect was seen in all subjects (Tanaka et al. 1972).

- Yagi et al. executed the double-blind, crossover designed trial to compare the efficacy of mazaticol to trihexyphenidyl and drometazine. Latter two agents had been commonly used in Japan at that time. Forty inpatients with anti-psychotropic drug induced extrapyramidal symptoms were recruited from seven hospitals. Primary diseases were schizophrenia, senile psychosis, mental retardation, and manic psychosis. Each number of patients was 37, 1, 1, and 1, respectively. The trial was 3-period, 3-treatment crossover design. One period was set as 2 weeks. The dosage of mazaticol, trihexyphenidyl, and, drometazine was 12 mg, 6 mg, and 75 mg per day, respectively. Two patients dropped out due to the worsening of psychiatric or physical symptom. One patient refused to take drugs. One patient discharged during trial. The efficacy rate of mazaticol, trihexyphenidyl, and drometazine was 78.94%, 92.30%, and 69.44%, respectively. Although there was a statistically significant difference between trihexyphenidyl and drometazine, mazaticol showed no difference compared to other two agents. There was no order effect among three periods. As to the efficacy to extrapyramidal symptoms, trihexyphenidyl was superior to mazaticol for akathisia and more effective to promethazine for salivary hypersecretion and face. There was no difference among three agents for the change of psychiatric symptoms during the trial. There was no severe side effect during the trial. Appearance probabilities of fatigue and dry mouth were rather higher in mazaticol. Yagi et al. concluded mazaticol was as effective as trihexyphenidyl and drometazine in treating the drug-induced extrapyramidal symptoms (Yagi et al. 1973).
- Fujimura also reported the double-blind clinical evaluation for mazaticol and amantadine. Eleven schizophrenia inpatients with parkinsonism were randomly assigned. The study was 2-period, 2-treatment crossover design. One period was set as 2 weeks. The dosage of mazaticol and amantadine was 12 mg and 300 mg, respectively. Parkinsonism was assessed in regard to akinesia, tremor, muscle rigidity, masked face, hypersalivation, akathisia, and dyskinesia. General improvement ratio of mazaticol and amantadine was 83.3% and 75.0%, respectively. But there was no statistical difference between two drugs. Mild side effects such as dry mouth, headache, and insomnia were seen in mazaticol treatment but there was no need to reduce or to stop the medication. As the improvement ratio of mazaticol for akinesia, rigidity, and tremor was superior to that of amantadine (mazaticol: 83.3%, 72.7%, 72.7%, amantadine: 58.3%, 63.6%, 54.5%), Fujimura considered that this result was due to the fact that mazaticol had both of anti-acetylcholinergic and dopaminergic activity (Fujimura 1976).
- Takesada et al. executed the double-blind, crossover designed trial to compare the efficacy of mazaticol and amantadine. Sixty-eight inpatients with parkinsonism were recruited from six hospitals. Primary diseases were schizophrenia, cerebral arteriosclerosis, atypical psychosis, and hysterical psychosis. Each number of patients was 63, 2, 2, and 1, respectively. The trial was placebo-controlled

2-period, 2-treatment crossover design. One period was set as 2 weeks. The dosage of mazaticol and amantadine was 12 mg and 300 mg per day, respectively. One patient dropped out due to the worsening of parkinsonism during the wash-out period. One patient refused to take drugs. One patient discharged in order to undergo hernia surgery. The general improvement rate of mazaticol and amantadine was 89.2% and 80.0%, respectively. Although there was no statistically significant difference between mazaticol and amantadine, mazaticol tended to be superior to amantadine. As to the efficacy to extrapyramidal symptoms, mazaticol was superior to amantadine for tremor, salivary hypersecretion, masked face, and akathisia. But no statistically significant difference was seen between two drugs. There was no severe side effect during the trial against these two medicines. Side effects of mazaticol included dizziness, dry mouth, headache, nausea, and insomnia. The number of patients who showed those side effects is 9, 5, 4, 4, and 4, respectively. Takesada discussed that combination therapy of mazaticol and levodopa is desirable because mazaticol is effective so that total dosage of levodopa could be saved and then the side effect of levodopa such as nausea, vomit, anorexia, depression, hallucination, and delusion could be inhibited (Takesada et al. 1977).

- Nakajima et al. reported the effect of mazaticol for 19 patients with anti-psychotropic drug induced extrapyramidal symptoms. Primary diseases were 14 schizophrenia, four atypical psychosis, one posttraumatic head injury, one obsessive-compulsive neurosis, and one exogenous reaction type psychosis. The dosage of mazaticol was 12 mg to 24 mg per day. Extrapyramidal symptoms were assessed for parkinsonism, akathisia, akinesia, and others. Seventeen patients showed improvement of symptoms. As to each symptom, 10 out of 13 patients with tremor improved. Eight out of 11 patients with muscle rigidity showed improvement. Nine out of 12 patients with bradykinesia revealed improvement. Other symptoms that appeared good response to mazaticol included salivary hypersecretion, anxiety, and akathisia. The general improvement rate was 89.5%. There was no severe side effect during the trial. The remarkable point of this study is that ten patients with showing bad response to other existing anticholinergic drugs mitigated symptoms after prescribing mazaticol (Nakajima and Matsuda 1986).

Side Effects/Adverse Reactions and Toxicology

Side Effects

According to the Pharmaceutical products interview form in Japan, the number of reported side effects is 296 out of 3852 (7.7%) since manufacturer and sales approval day on April 1986. Major symptoms are as below;

Dizziness and wobble: 64 (1.7%), Dry mouth: 49 (1.3%), Nausea and vomit: 39 (1.0%).

Syndrome malin. There are reports of cases that cessation of antiparkinsonian drug administered with other drugs such as antipsychotics, antidepressants, and

dopaminergic antiparkinsonians caused the syndrome malin. Symptoms of syndrome malin are characterized by fever, akinesia, muscle rigidity, involuntary movement, tachycardia, difficulty of swallowing, blood pressure variation, and perspiration.

Toxicology

Chronic toxicity study in rats revealed resemblance to those of atropine. After oral administration of mazaticol at the dosages of 100, 50, 25, 12.5 mg/kg/day for 6 months, 100 and 50 mg/kg/day administrated groups showed inhibition of growth of rats (Kawai et al. 1974).

Teratogenic effect study in mice and rats showed no effect of mazaticol. However, after oral administration of mazaticol at doses of 100, 50, 5 mg/kg for mice from day 7 to 12 of pregnancy and 200, 100, 5 mg/kg for rats from day 9 to 14 of pregnancy, maternal body weight gain and fetal body weight showed significant reductions. There was a correlation between the inhibitory effect on maternal body weights and on the fetal body weights (Yamaguchi et al. 1974).

Contraindications

- Patients with glaucoma. Anticholinergic effect may increase intraocular tension and as a sequence, may worsen the glaucoma.
- Person who has an allergy to this agent.
- Patients with myasthenia gravis. The anticholinergic effect may cause hypotonia and may worsen the symptom of myasthenia gravis.
- Patients with urinary obstruction such as prostatomegaly. Anticholinergic effect may cause relaxing on the bladder smooth muscle and contraction of urinary bladder muscular sphincter, as a result, may worsen dysuria.

Careful Administration

- Patients with tachycardia or palpitation. Anticholinergic effect causes a sympathetic nerve predominance, as a sequence, might worsen arrythmia.
- Patients with renal disorders or hepatic disorders. Prolonged metabolism and excretion of drug may enhance the drug effects.
- Elderly. Decreased physiological function of aged person may easy to cause psychiatric symptoms such as delirium, anxiety, and dizziness and dry mouth. It is alerted in the pharmaceutical products interview form that dosage for the elderly should be carefully considered because the aged people are susceptible to those side effects. In some studies, it is reported that mazaticol might cause various psychiatric symptoms compared to other antiparkinsonian drugs (Saito et al. 1982; Suitsu 1992).

- Patients in high-temperature environment. Anticholinergic effect causes perspiration suppression, and as a sequent, causes the dysregulation of temperature control.
- Patients with dehydration or malnutrition. In such patients, syndrome malin is more likely to be caused.

Attention

- Low dose of Initial prescription and gradual increase of mazaticol are recommended. Increment is recommended to the maximum tolerable dose and then decide the usual dosage as a little bit smaller as the maximum dose. In case of switching other drug to mazaticol, dosage teparing of other agent and gradual increase of mazaticol are also recommended. Because the occurrence of side effects of anticholinergic agents is dose dependent. Sudden cessation of prescription is dangerous.
- Routine gonioscopy and tonometry are recommended.
- Driving is not recommended. Anticholinergic effect may cause sleepiness, decreased concentration, and decrease reaction response.

Combination Therapy: Interactions

- Anticholinergic agents (phenothiazine compound, tricyclic antidepressant, atropine sulfate hydrate, butyl scopolamine bromide, timepidium bromide hydrate) may enhance mazaticol's anticholinergic effect such as hypohidrosis and intestinal palsy.
- Central nervous system depressant (phenothiazine compounds, tricyclic antidepressants, MAO inhibitors) may enhance mazaticol's mental inhibitory action.

Cross-References

► Piroheptine for Treating Parkinson
► Trihexyphenydyl for Treating Parkinson

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