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Author(s)	NAGASE, MASAO; TANIMURA, HIROSHI; TAKENAKA, MASAFUMI; SETOYAMA, MOTOICHI; KAMATA, TOSHIO; MUKAIHARA, SUMIO; MARUYAMA, KEISUKE; KUMADA, KAORU; HIKASA, YORINORI
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Biliary Distention Pain and its Medical Treatment

MASAO NAGASE, HIROSHI TANIMURA, MASAFUMI TAKENAKA,
MOTOICHI SETOYAMA, TOSHIO KAMATA, SUMIO MUKAIHARA,
KEISUKE MARUYAMA, KAORU KUMADA and YORINORI HIKASA.

The 2nd Department of Surgery, Kyoto University, School of Medicine,

(Director : Prof. Dr. YORINORI HIKASA)

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I. Introduction

Patients suffering from biliary diseases are increasingly seen both in medical and in surgical clinics, mainly because of the increased incidences of cholesterol gallstones in recent Japan due to westernization of dietary habits.

Mechanisms of symptoms caused by biliary diseases are discussed briefly and clinical effects of trepibutone, a newly produced drug for relief of biliary pain, are mentioned.

II. Mechanisms of biliary symptoms

Main symptoms caused by biliary diseases are as follows : 1) colicky pain due to spasm of the gallbladder, 2) continuous distention pain due to elevated intraductal pressure, 3) shoulder or back pain due to reflex and 4) nausea, vomiting and so on due to autonomic nervous reflexes.

It seems unlikely that augmented peristalsis of the common bile duct causes colicky pain since its wall has no sufficient smooth muscles for inducing definite peristalsis. Spasm of the sphincter of Oddi by itself induces no pain. Distention of the bile ducts due to elevated intraductal pressure is probably the most important cause of continuous biliary pain¹⁾.

Spasmolytic agents are definitely effective for colicky pain but not for other symptoms. For relief of continuous distention pain, flopropione (Cospanon®), hymecromone (Hymecol®) etc., which relieve spasms of the sphincter of Oddi, lower the elevated intraductal pressure and increase the bile flow, have been used with moderately good results.

III. Pharmacological features of trepibutone

Recently the authors have had opportunity to use trepibutone, a newly produced drug, which has a similar chemical structure (Fig. 1) and pharmacological effects to flopropione and hymecromone. Trepibutone relaxes the sphincter of Oddi by direct action on smooth muscles and lowers the intraductal pressure. It antagonizes spasm-inducing action of

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Present address : Second Department of Surgery, Kyoto University, School of Medicine. Sakyo-ku, Kyoto, 606, Japan.

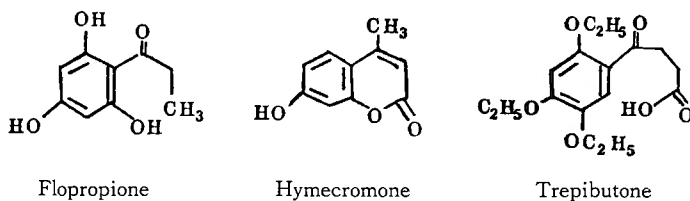


Fig. 1 Chemical structure of relaxants of Oddi's sphincter.

Table 1. Clinical effects of trepibutone on continuous distention pain

Disease	Effects	Excellent	Good	Fair	None	Total
Cholelithiasis		11	3	9	2	25
Biliary dyskinesia		8	3	2	3	16
Postcholecystectomy syndrome		13	11	7	1	32
		32	17	18	6	73

Table 2. Improvement of biliary symptoms (73 cases)

Symptoms	Excellent	Good	Fair	Poor	aggravated
Spontaneous pain	47.5%	23.8%	21.3%	7.5%	0%
Gastrointestinal symptoms	28.8	13.8	25.0	32.5	0
Physical examination	33.8	11.3	17.5	37.5	0

morphine. It promotes bile secretion from the liver independently of bile acid secretion.

IV. Clinical evaluation of trepibutone

In September 1975, the authors have organized "The Group for Research of Cholelithiasis" consisted of general surgeons of Kyoto University Hospital and of 36 affiliated hospitals²⁾ and have collected and reviewed the 2,144 cases operated on for cholelithiasis during the last 20 months. In parallel with this collective review the clinical usefulness of trepibutone was evaluated in nine hospitals, which were listed up in the acknowledgment.

A tablet containing 40 mg of trepibutone was given three times a day orally to 73 patients suffering from cholelithiasis, biliary dyskinesia and postcholecystectomy syndrome. Some patients were treated with spasmolytic agents at times when they were seized by colicky attacks. Duration of drug administration ranged from two weeks to twenty weeks, averaging 5.8 weeks.

Effects of the drug for continuous distention pain are shown in Table 1. Almost same effects were observed for dyspeptic symptoms and for abdominal tenderness as shown in Table 2.

As side effects observed were skin eruption in one patient and general malaise in

another, probably due to drug administration, and the drug was discontinued in these cases.

Liver functions were examined every two weeks in most patients, and no remarkable changes attributable to the drug were observed in any cases.

V. Discussion

While diagnostic techniques for biliary diseases have recently progressed markedly, their faculties are still far inferior than those for gastrointestinal diseases which can detect so small lesions as early cancers by double-contrast rentogenography and by endoscopy. Primary cancer of the gallbladder, for example, can be diagnosed only in its advanced stage or may be found out incidentally at surgery for gallstones. Accurate diagnosis of the so-called biliary dyskinesia and postcholecystectomy syndrome can hardly be achieved by ordinarily available diagnostic methods. Moreover, significance of the biliary dyskinesia and postcholecystectomy syndrome as real clinical entities is still in controversy. Our impression is that these designations should be abolished in accordance with progress of diagnostic faculties and with further clarification of biliary physiology.

At present one should be strictly cautious in attributing any patient's complaints to organic and/or functional distortion of the biliary tracts and should also always exclude other abdominal lesions which may cause similar symptoms, by means of rentogenologic and endoscopic studies of the gastrointestinal tracts. Occasionally diagnosis by specific medical treatments (*Diagnosis ex juvantibus*) may be needed for equivocal patients.

However, needs for good agents for relief of biliary symptoms, especially of distention pain, are increasing in clinical practice, because of the increasing incidences of biliary diseases.

Two of the present authors (Tanimura, H. and Takenaka, M.) have clearly demonstrated that trepibutone has a definite effect of relieving spasm of the sphincter of Oddi and of lowering intraductal pressure by measurements of intraductal pressure through choledochal T-tubes (pharmaco-bilio-manometry) in human beings³⁾.

Our impression obtained by strict appraisals of data collected from 73 patients given trepibutone are as follows.

- 1) Trepibutone are fairly effective for relief of distention pain due to elevated intraductal pressure.
- 2) Administration of the drug for two weeks or more is necessary for its effectiveness.
- 3) Side effects of minor significance is very rarely seen.
- 4) The drug has no adverse effects on liver function even if it is given for as long as twenty weeks.

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和文抄録

胆道痛の発生機序と Trepibutone の効果について

京都大学医学部外科学教室第2講座

長瀬 正夫, 谷村 弘, 瀬戸山元一, 鎌田 寿夫
向原 純雄, 丸山 啓介, 熊田 馨, 日笠 頼則

胆道疾患による主な症状は、感染と黄疸を除けば、次の4つに分けることができる。

1) 胆嚢壁の平滑筋の攣縮による仙痛（総胆管壁には仙痛をおこすにあたいする程の平滑筋は存在しない）、2) 胆管内圧の上昇による持続的な伸展痛、3) 関連痛としての背痛、肩痛、4) 自律神経性反射による悪心、嘔吐などである。

仙痛に対しては鎮痙剤がよく奏効するが、胆道内圧の上昇による伸展痛に対しては余り効果がない。

今回、われわれは 1) Oddi 氏括約筋に対して弛緩作用を有し、2) 胆管内圧をさげ、3) 胆汁分泌を促進

する薬剤 Trepibutone を胆石症25例、いわゆる胆道ヂスキネジー16例、胆嚢切除後症候群32例、合計73例に使用し、そのうちの51例において持続性伸展痛の中等度以上の改善をみとめた。その他の胃腸症状や腹部圧痛についてもほぼ同様の効果がみられた。

薬剤の使用期間は2~20週、平均5.8週であったが、副作用としては発疹1例、全身倦怠感1例をみとめたのみであった。また本剤の投与によって肝機能が悪化したと思われるものは1例もなかった。

したがって、Trepibutone は胆管内圧の上昇による症状に対して使用して良い薬剤であると考えられる。