

行政院國家科學委員會補助專題研究計畫成果報告

自製鋇劑混合液以作為電腦斷層攝影口服顯影劑之研發

計畫類別： 個別型計畫     整合型計畫

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## 中文摘要

本研究主要目的在發展一種安全、便宜且容易泡製的自製鋇劑混合液以作腹部電腦斷層攝影檢查時的口服顯影劑。此類顯影劑目前在臺灣並無進口。本鋇劑混合液由低量硫化鋇及兩種阻抗性澱粉 ( resistant starch ) Xanthan gelose 50 所組成。體外實驗發現其穩定度極佳，在沖泡後 72 小時仍然均勻懸浮且沒有沉澱產生。體內實驗發現此鋇劑混合液均勻分布在腸胃道

各部，其顯影效果極佳，其所接觸之腸胃壁可見，且無明顯假影產生。病人在吞服時至 24 小時後追蹤並無嘔吐、腹痛及腹瀉等副作用產生。另一優點為此自製鋇劑混合液極為便宜，以平均一次腹部電腦斷層攝影檢查以飲用 900 毫升鋇劑混合液為例，只需新台幣 10 圓。

關鍵詞：

鋇劑混合液，腹部電腦斷層攝影，阻抗性澱粉

## 英文摘要

The objective of this study was to develop a safe, cheap, and easily prepared dilute barium mixture as an oral contrast agent for abdominal computed tomography examinations which is currently not available in Taiwan at this time. The barium mixture we developed consists of a low concentration of barium sulfate and resistant starches including Xanthan gum and gelose 50. An in vitro study was performed and it showed that the stability of this newly developed formula is excellent. Further in vivo studies revealed that the opacification of this agent in various parts of the bowel loops is adequate and without the formation of sedimentation or perturbing artifacts. No immediate or delayed side effects were found after the ingestion of this barium mixture.

### Key words:

Barium mixture, computed tomography, resistant starch

## INTRODUCTION

Opacification of the bowel loops is important in abdominal computed tomography (CT) to prevent misinterpretation. Both a dilute water-soluble iodinated contrast agent and dilute barium can be used for this expressed purpose [1-3]. Typically, dilute barium needs suspending agents to decrease the rapid sedimentation of barium sulfate. Although there are various kinds of suspending agents available on the market, they are usually expensive and the chemical formulae are not readily known to physicians. Recently, we developed our own barium mixture which is very inexpensive and can be easily prepared. The motivation for us to develop our own mixture is that commercially manufactured dilute barium is not available in Taiwan. Moreover, we intended to find a formula of dilute barium which is lower in price than current products available on the market.

## **MATERIALS AND METHODS**

### **Composition**

This new barium mixture consists of a low concentration of barium sulfate, Xanthan gum and gelose 50. Both Xanthan gum and gelose 50 are high molecular weight "resistant starches" commonly used as food additives. Studies show that they are stable in an acid environment such as those involving gastric secretion, and that they can not be digested by most human gastrointestinal tract enzymes. The preparation of this newly developed mixture is simple: various concentrations of barium sulfate (0.5 % -2 % wt/vol), Xanthan gum (0.3 % -0.5 % wt/vol) and gelose (3 % -5 % wt/vol) were mixed electrically for 30 seconds to form a viscous barium mixture.

### **In vitro Study**

Four different ratios of barium mixture were tested in vitro. Formula 1 consisted of 2 % barium sulfate, 0.5 % Xanthan gum and 4 % gelose 50. Formula 2 consisted of 1.2 % barium sulfate, 0.35 % Xanthan gum and 5 % gellse 50. Formula 3 consisted of 1.5 % barium sulfate, 0.4 % Xanthan and 3 % gelose 50. Formula 4 consisted of 0.5% barium sulfate, 0.3% Xanthan gum, and 3% gelose 50. The sedimentation rates, homogeneity and density of these four formulae were evaluated at one hour, two hours, and four hours after the preparation.

### **In vivo Study**

Over a period of six months, 50 patients who received a CT examination of the abdomen due to various conditions such as cervical carcinoma, lymphoma and colon carcinoma, were included randomly to this study. All of these patients were fully notified before the study and informed

consents were obtained. Four different ratios of the barium mixture listed above were applied to the first 20 patients (each formula for 5 patients). The other 30 patients received Formula 2 only. All the studies were undertaken in either a Picker PQ2000 CT scanner (Picker International, Cleveland, Ohio) or a Siemens Somaton DR3CT scanner (Siemens, Erlangen, Germany). When the study was erformedm,600 ml of the mixture was taken one and a half hours before, followed by 300 ml taken immediately before the CT examination. The sedimentation, density measurement, opacification of the bowel loops, transit time, and safety after ingestion were evaluated. To evaluate the feasibility of the barium mixture, the images of these 30patients and other 30 patients who received the 2.6 % vol/vol diluted water soluble mixture (Telebrix 38) as the oral contrast agent for the abdominal CT examination were compared. The artifact formation was later evaluated blindly by two senior radiologists. The artifacts were classified as "no artifact". "slight artifact" or "marked artifact". The palatability of the mixture to the patients was evaluated immediately after ingestion. Side effects were evaluated immediately and at the next day of the examination whenever possible.

## **RESULTS**

### **In vitro Study**

The barium mixture remained homogeneous without sedimentation in all of the four formulas. Formula 2 was evaluated 72 hours after the preparation and at that time it still showed no evidence of sedimentation. The density measurement appeared to be

different in the four formulas (Table 1) and seemed to be primarily dependent on the concentration of the barium sulfate and possibly, also by the small air bubbles in the mixture.

### **Optimization of Dilute Barium Mixture**

After the *in vitro* and *in vivo* tests using the different ratios of these three constituents, Formula 2 was found to be adequate for clinical usage. Our results showed that when we increased the concentration of the Xanthan gum, the viscosity was increased, and the transit time in the bowel loops was slowed down.

### **In vivo Study**

Our new barium mixture appeared to fill the stomach and most of the small bowel loops well (Fig 1-3). The density of this new mixture in the stomach and the small bowel loops ranged from 250 to 800 H.U. depending on the location and the individual patient's condition including the presence of gastric secretion or abundant bowel fluid. In our mixture, there was no evidence of flocculation or sedimentation. Also, there were no disturbing streaking artifacts which might affect our diagnosis (Table 2). The labeling of the bowel loops is especially good in the duodenum and proximal jejunum. The transit time from the stomach to the right hemicolon ranged from 1.5 to 2.5 hours. In our study of 50 patients, no patient suffered from immediate or delayed reactions like vomiting, diarrhea, or abdominal pain. Although no artificial flavors or sweeteners were added, its palatability was acceptable to most patients. Only one patient having nauseous sensation did not take the mixture.

## **DISCUSSION**

Abdominal CT examinations require opacification of the gastrointestinal tracts, as non-opacified loops might be mistaken for a soft tissue mass or a lymph node. Apart from iodinated contrast agents, dilute barium sulfate can also be used for this purpose. Barium sulfate has, over a long time, been used for studies of the gastrointestinal tract. It has been found to be non-absorbable, is inert to the bowel loops and does not affect the peristalsis or cause osmotic change.

To act as a contrast agent for CT examinations, barium sulfate needs adequate suspending agents to avoid its fast sedimentation and streaking artifact. Although there are already various kinds of commercially available products, they are usually expensive. Moreover, the key constituent of suspending agents in dilute barium mixture is always kept as a company secret that is known only to the manufacturers. Our *in vitro* study showed that even a low concentration of barium sulfate, when mixed only with water, settled down rapidly within seconds and can cause disturbing artifacts in CT. It appears that whatever is used as a suspending agent for barium mixture in abdominal CT examinations, it needs to be pH resistant, and digestively enzyme-resistant. In our study, we found that Xanthan gum and gelose 50 fulfil these requirements well. Xanthan gum, which is produced from *Xanthomonas campestris* and is considered a resistant starch, consists of D-glucose, D-mannose, and D-glucuronic acid. The molecular weight of this starch is about one million. It can be found as a food additive for products

we find in our daily life such as bread, canned soup, spaghetti, breakfast cereals, dairy desserts, pastries, and pasta. The solubility of Xanthan gum is equal at temperatures ranging from 20 to 95 °C, which makes the preparation of the barium mixture with this suspending agent at room temperature quite easy. Xanthan gum not only remains stable when the pH value ranges from 2 to 13, but also resistant to the digestion of proteinase, lipase, and collagenase. Gelose 50, coming from a specially developed breed of maize, bears the similar characteristics as Xanthan gum. The opacification of a dilute barium mixture for bowel loops in CT has been shown to be comparable to that of a dilute iodinated contrasting agent [3]. The palatability of barium mixture including taste and ease of swallowing was also similar or even superior to that of water soluble contrast agents. Although no artificial flavors or sweeteners were added to the formula, our newly developed barium was acceptable to most patients. However, its palatability can be expected to be much improved when the formula is further refined with flavor or sweetener additives. An important point worth mentioning about this newly developed mixture is its low cost. The cost to produce 900 ml mixture for one patient is NT \$ 10. This cost is three to fifty times cheaper than currently available water-soluble contrast agents or dilute barium on the market [4]. In the preliminary in vivo study, although mild artifacts were observed in about one third of our patients, it did not reduce our diagnostic ability. The artifacts were not necessarily related to the barium

mixture itself. Bowel movement and air-fluid interface might also account for this finding. Furthermore, the artifacts noted in our patients using the barium mixture were similar to that caused by the dilute water soluble contrast agent. Although the preliminary results are promising, there is still one problem left to be resolved. The transit time of this new barium mixture is slower when compared with that of water soluble agents and barium mixtures on the market which are stated to have a transit time of less than one and a half hours from the stomach to the right hemicolon. The reason for the difference might be the motility-promoting agents, like sorbitol, which have been added to the products.

In conclusion, we have developed a new dilute barium formula which is safe, inexpensive and easily prepared for use with abdominal CT examinations. Our preliminary results show that Xanthan gum and gelose 50 act very well as suspending agents for barium sulfate. Further studies based on a larger patient population are needed to evaluate its clinical potential as a routine oral contrast agent for abdominal CT examinations.

## REFERENCES

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**Table 1.** Sedimentation and density measurement of four barium mixtures in vitro

| Formula | Time after preparation |           |            |
|---------|------------------------|-----------|------------|
|         | one hour               | two hours | four hours |
| 1       | No/288*                | No/260    | No/250     |
| 2       | No/192                 | No/190    | No/220     |
| 3       | No/220                 | No/200    | No/230     |
| 4       | No/83                  | No/72     | No/107     |

\*The unit of density measurement is HU.

No: no sedimentation

**Table 2.** Evaluation of artifacts in 30 patients using barium mixture or Telebrix 38 as oral contrast agent for abdominal CT examination

| Artifact | Telebrix 38 | Barium mixture |
|----------|-------------|----------------|
| No       | 17          | 18             |
| Slight   | 13          | 12             |
| Marked   | 0           | 0              |

CT: computed tomography.

### 成果自評

本研究計畫在一年的實行期間已完成此項新試劑之人體內及人體外之評估。對於其診斷效果也已作了客觀的鑑定，並與水溶性顯影劑作了比較，初步結果顯示診斷效果良好、安全性高且成本低廉。

可惜原本欲達成之增進其在腸道通過速度以減少病人服用後之等待時間的目標並未實現，理想之促進劑目前仍在試驗中。另外溶液之準備及沖泡工作如何簡化，也是另一課題。唯如果此試劑日後能大量製造並上市則預計當如喝“易開罐”果汁般的容易。