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Does folinic acid have a choleretic effect on humans?

İnsanlarda folinik asidin koloretik etkisi var mı?

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Background/aims: *The aim of this study was to clarify whether folinic acid has any choleretic effect in humans, as observed by Kajiyama et al. in both clinical and experimental studies.* ***Methods:*** *The choleretic effect of folinic acid was analyzed prospectively in a subgroup of patients who had external biliary catheters with periampullary tumors causing complete biliary obstruction. Folinic acid (50mgl day) was administered twice with a 24-hour interval between each dose. Daily bile volume was then recorded on the three consecutive days following the first dose of folinic acid. Mean bile flows (basal output=mean bile volume of four days) before and after (fifth, sixth and seventh days) the initiation of folinic acid administration were then compared.* ***Results:*** *Mean bile volumes were determined as baseline output: 669.20+235.18, 5th day=: 6G8.63±235.26, sixth day: 670.45±235.08, and seventh day: 670.00+235.11. No significant difference in daily bile volumes before and after folinic acid administration was detected (p>0.05).* ***Conclusion:*** *No choleretic effect of intravenous folinic acid administration was observed in this prospective clinical study. This finding was contrary to our previous study on this subject.*

Keywords: Folinic acid, bile production, choleresis

Amaç: *Bu çalışmada, daha önce Kajiyama ve arkadaşlarının bir klinik gözleme dayanarak yaptıkları deneysel çalışmada gösterdikleri, folinik asidin koloretik etkisinin tekrar değerlendirilmesi amaçlanmıştır.* ***Yöntem:*** *Folinik asidin koloretik etkisi, tam safra yolu tıkanıklığına yol açmış periampüller bölge tümörü nedeniyle eksternal safra drenajı olan hasta grubunda çalışıldı. Hastalara 24 saat ara ile 2 kez 50 mg folinik asid intravenöz olarak verildi, ilaç verilmeden önce 4 gün ve ilacın ilk verilmesini takip eden 3 gün boyunca hastaların safra drenajları kaydedildi. Folinik asidin verilmesinden sonraki günlerde ölçülen safra drenajları bazal ortalama safra drenajı ile karşılaştırıldı.* ***Bulgular:*** *Ortalama bazal safra drenajı 669.20+235.18 ml, folinik asidin ilk verildiği gün 668.63+235.26 mi, ikinci gün 670.45+235.08 ml, üçüncü gün ise 670.00+235.11 rai bulundu. Folinik asid öncesi ve sonraki günler arasında safra drenajı açısından istatistiksel anlamlı bir fark bulunmadı (p>0.05).* ***Sonuç:*** *Bu çalışmada intravenöz verilen folinik asidin koloretik bir etkisi gözlenmemiştir. Bu bulgu daha önce yapılan ve literatürde yayınlanan çalışma ile çelişkilidir.*

Anahtar Kelimeler: Folinik asid, safra yapımı, kolorezis

INTRODUCTION

Folinic acid, the reduced form of folic acid, is currently used both in the prevention of the acute toxic effects of folate antimetabolytes, such as methotrexate or primethamine and also for treatment of chronic macrocytic anemia caused by these drugs. Folinic acid, also called leucovorin or the citrovorum factor, is often used to potentialize the antineoplastic effect of 5-fluorouracile (5-FU) as a chemical modulator (1).

Kajiyama et al. reported an incidental clinical observation of an improvement in liver functions and increased bile secretions the day following a chemotherapy protocol including 5-FU and folinic acid in 56 advanced gastric carcinoma patients. However, it is well known that 5-FU has the potential effect of hepatotoxicity and this has been interpreted as a possible choleretic effect of folinic acid (2). The results of an experimental animal study designed to confirm this interesting observation and explain the mechanism were reported by the same authors. Similar findings of increased bile volume and total bile acid production were reported following intraperitoneal administration of folinic acid to rats (3).

The patient with advanced cancer and deteriorating liver functions and the responsible doctor are both faced with a dilemma when an antineoplastic therapy protocol with known hepatotoxic side

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effects is required. In such cases, there is always a risk of deterioration in the patient's status, although the only aim of treatment is to improve the condition. If the choleretic effect of folinic acid could be confirmed, decisions about chemotherapy protocols for the cancer patients with jaundice and abnormal liver function tests would be easier. Moreover, this drug could be placed on the agenda of treatment options for patients with chronic liver disease, primary biliary cirrhosis or liver transplantations and potentially become a new option in the treatment of jaundice or to create an improvement overall liver functions.

Although many cancer patients, some with abnormal liver functions, had been treated with folinic acid included in chemotherapy protocols in our surgical oncology department, we had not observed the beneficial effect of choleresis, as stated by Kajiyama et al. and no other report in the medical literature either supporting or refuting this observation could be found. This study was therefore undertaken to clarify this observation with a prospective clinical human study on patients with an external biliary drainage catheter for complete obstructing periampullary tumours.

MATERIALS AND METHODS

Eleven patients with periampular tumors causing complete obstruction and with external biliary drainage catheters for the palliative treatment of jaundice were included in the study. The male-female ratio was 8/3 and the mean age of patients was 52.8±10.4 (range; 43-77 years). In all patients, the external biliary drainage catheters had been inserted into the most dilated intraparanchymal bile duct with an ultrasonography guided percutaneous transhepatic technique. The mean time interval between catheter insertion and the study was 18±-4 days and the mean total and direct serum bilirubin levels of the patients were 6.3±-1.8 and 4.8±-2.1 mg/dL respectively. Institutional ethics committee approval and informed consent were obtained for each patient. Inclusion criteria were as follows: complete obstruction in the common bile duct, presence of an external biliary drainage catheter, no previous cholangitis episodes and stable bile flow in the previous four consecutive days. Patients with daily bile flow alterations of more than 5% were accepted as unstable and were excluded from the study. After recording of daily bile flow volumes for four consecutive days, folinic acid (50 mg/day) was administered by slow intravenous infusion and 24 hours later the same dosage was repeated by the same route. Recording of bile flow was continued for three days after the first folinic acid administration. The pre-and post treatment mean daily bile drainages were then compared in order to investigate the choleretic effect of folinic acid. The paired t test was used for statistical analysis.

RESULTS

The daily bile flow volumes of seven days for each of the 11 patients are illustrated in Table 1, with the latter three representing post-treatment values. The mean bile volume of the four pre-treatment days was accepted as the basaline bile production and compared with the mean value of the last three days (Table 2). No significant difference was observed regarding bile volumes of the pre- and post treatment periods (p>0.05). The serum bilirubin levels also remained stable during the study period. Thus in this clinical study, our findings did not correlate with the previous experimental study and were unable to demonstrate the choleretic effect of folinic acid.

Table 1. Daily bile drainages of patients four days before and three days after folinic acid administration

Patients	Day 1 ml/day	Day 2 ml/day	Day 3 ml/day	Day 4 ml/day	Day 5 ml/day	Day 6 ml/day	Day 7 ml/day
1	250	240	240	250	230	240	220
2	850	800	830	850	825	875	800
3	750	760	750	740	760	730	750
4	1020	980	1000	1020	1000	1040	1030
5	630	650	650	620	620	630	640
6	950	1000	970	980	950	1020	980
7	750	760	750	740	760	730	750
8	500	480	500	510	520	480	500
9	720	700	730	700	740	680	730
10	580	600	570	580	590	570	600
11	380	370	375	370	360	380	370

Table 2. Mean daily bile flow volumes baseline and following folinic acid administration

Day	Mean bile volume (ml)	
Baseline (Dayl-4)	669.20±235.18	
Day 5	668.63±235.26	p>0.05
Day 6	670.45±235.08	p>0.05
Day 7	670.00±235.11	p>0.05

DISCUSSION

Folinic acid is widely used to prevent the toxic effects of methotrexate and to strengthen the antineoplastic effect of 5-fluorouracile (1). In advanced gastric carcinoma patients receiving 5-FU and folinic acid, Kajiyama et al observed an improvement in liver functions and diminished jaundice and had reported this incidental finding in 1996 (2). As it was known that 5-FU is a hepatotoxic agent, the authors had attributed that beneficial effect to the folinic acid. Later, an experimental study was designed and undertaken by the same authors to confirm this incidental clinical finding and to explain the mechanism. In the study, they ligated the distal side and cannulated the common bile duct of 10 rats and divided them into two groups. Five rats received 1 mg/kg of folinic acid intraperitoneally and the remaining five received 0.9% NaCl by the same route. The bile drainage as well as bile acid concentration were found to be increased in the folinic acid group and the choleretic effect of folinic acid was interpreted as a bile acid dependent mechanism (3). This observation, which was confirmed with the experimental study by the same authors, was of great surprise to the present authors. Although many gastric ano-colorectal cancer patients with abnormal liver function tests due to liver metastasis, hepatosteatosis or hepatotoxic drugs had been treated with the same chemotherapy protocol in our surgical oncology department, we were unaware of this beneficial side effect. It was therefore decided to re-evaluate this observation with a prospective clinical human study. The most reliable and convenient human model was determined as those patients with periampullary tumours causing total biliary obstruction and with external biliary drainage catheters. In those patients who volunteered to particupate in the study, a catheter was inserted via a percutaneous transhepatic route for the palliation of jaundice and those with a daily stable bile production were included. No difference was observed in the bile flows of patients after administration of folinic acid, which shows that folinic acid has no choleretic effect in humans. Although the daily bile flows of each patient had remained stable, there were significant flow differences between patients, ranging 220 to 1040 ml/day. The degree of intrahepatic cholestasis and the integrity of the drained ductus with the entire biliary ductal system are possible explanations for this difference.

In this study, folinic acid was administered intravenously as it is the routine method of administration during antineoplastic therapy; in the experimental rat model use of the intraperitoneal route may have caused contradictory results. It is well known that patients with advanced or recurrent gastric carcinoma who have obstructive jaundice caused by extrahepatic biliary metastases normally respond to combination chemotherapy protocols which induce shrinkage of the metastatic lymph nodes. This temporary reopening of the biliary tract is a mechanical effect and completely irrelevant to the choleresis (4). Abnormal liver functions and jaundice may cause considerable distress. In the planning of antineoplastic therapy, it is therefore very important to include agents which improve liver function in this patient group. One agent, which has been investigated for its choleretic effect, is insulin-like growth factor-I (IGF-I). This is an endogenous growth factor produced by the liver, which promotes growth and has metabolic effects like insulin. In an experimental study, it was observed that administration of exogenous IGF-I cause increased bile flow and biliary acid secretion. Later, hypophysectomized rats were used in an attempt to clarify the relationship between IGF-I and bile acid secretion and decreased bile flow and biliary acid secretion were accomplished to the decreased IGF-I levels. A partial response was observed by giving exogenous IGF-I in the following week and the choleretic effect of IGF-I was emphasized (5) later, the same authors investigated the choleretic effect and its relationship with the IGF-I levels of two major immunosuppressive drugs for liver transplantation, FK506 (tacrolimus) and cyclosporine A, in an experimental rat model. Adminisration of intavenous FK-506 caused a marked increase in bile flow while cyclosporine A had the opposite effect. The plasma IGF-I levels were increased 30 minutes after a single intravenous dose of FK506. Oral administration of the drug for one week had shown the same effect and both the plasma and hepatic levels of IGF-I were increased, suggesting that a stimulation of hepatic IGF-I production by FK506 may contribute to its choleretic profile (6).

In an other experimental study, the effects of piperacillin administration on bile flow and biliary lipid secretion were studied in rats. Intravenous injection of piperacillin at doses ranging from 0.3 to 3.0 mmol/kg of bodyweight led to an increase in its biliary concentration and excretion rate.

Excretion of the antibiotic into bile was associated with a marked choleresis. These results indicate that acute administration of piperacillin in the rat induces a marked choleresis by stimulating bile acid-independent bile flow (7).

Although the choleretic effect of folinic acid was not demonstrated in our study as previously suggested by other authors, the study should be repeated in large patient groups with the addition of bile and IGF-I level analysis in order to clarify the contradictory results.

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