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Safety Pilot Study on Doctors Intravenous UDCA Self-Infusion among "The Doctor-Care-Yourself" Network

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Abstract:- The self-experimental procedures performed by doctors on their own, before (or instead of) extending the investigation to their patients is a very well known and ethical practice for the progress of medical diagnosis and therapies.

In the Doctor-Care-Yourself Network (born in University of Modena medical school, Italy), this issue is formally part of the duties of participants.

Our paper describes a self-experiment on intravenous perfusion of biliary salts in healthy doctors to verify the safety of different dosages, before trying them on the patients. The inventor of the parenteral treatment preliminary submitted himself only at first, to verify the feasibility and possible untoward effect of the treatment.

Subsequently, after this first positive self-experience, other three colleagues spontaneously joined the same protocol, which was confirmed to be absolutely safe and optimally tolerated.

I. INTRODUCTION

A few years ago looking around at the doctors behaviour along their professional and personal life, I realized that so many colleagues had diverted from the right way slipping into vicious circles, drug addiction, memory loss, depression, etc for many different reasons, and that no institution was taking care of them **[1-2]**.

I founded at that time in my University an ethical independent (still existing) hospital doctors Network named "*Doctor Care Yourself*" aiming at maintaining excellent psycho-physical and cognitive conditions (fitness and wellness) of the caregivers along the years of the practice through self-administration of health surveillance protocols (cancer, cardiovascular, respiratory, and mental periodical screenings), active regular physical activity, nutritional balanced and tailored lifestyle, multimodal individual artistic expressions, etc, in order to effectively neutralize the institution burnout, and cognitive deterioration in the ageing progress **[3]**.

In this Network, we strongly encourage the self-experimentation of new drugs or nutraceuticals, recruiting group of doctors affected by the same health problem (i.e. hypertension, diabetes etc) in order to be themselves as well as their patients careful and accurate monitors of any benefit or detrimental effects, and subsequently the best effective counselors of their patients on the use of the challenged drug and more generally of the disease management **[4].**

Furthermore, in our Network we regularly perform experimental studies for tailored therapies in some orphan area or for selected cases, and our problem solving strategy sometimes is concluded with original drug patents or galenic prescription to pharmacies.

In 2002, up to 2004, we met a small cluster of doctors affected by liver failure with jaundice and we planned to develop and try a new original therapy for liver insufficiency based on a parenteral administration of bile salts instead of their oral prescription.

Our concept was that this organ displays several homeostatic self-beneficial effects through the bile salts (BS) recirculation (they are in fact produced in biliary canaliculus, by the biliary cells, secreted into the gut and then reuptaken and conjugated after active interaction with the microflora, and with ingested food for digestion).

Before our clinical investigations, nobody had explored whether oral delivery of bile salts might successfully be switched to intravenous administration and what real advantages might have been achieved changing the delivery route.

We have conceived the parenteral treatment hypothesis instead of the oral on the basis that:

- The oral charge involves a limited amount of BS,
- Quite often the specific indication of oral bile salts treatment, for liver function restoration, cannot be administered due to the bad digestive conditions of the patients, such as:
  - Stenosis or obstructing tumours of the GI tract enclosed the pancreas, pancreatitis, liver injury,
  - Severe bowel impairment (stenosis, IBD, Chron, ulcerative colitis, diverticulitis),
  - Prolonged starvation,
  - Mandatory parenteral nutrition in intensive care units.

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This issue is critical in a great number of cancer patients especially during chemotherapy.

We had experimentally (RATS) observed in 1984 with orally administered fluorescent biliary salts that they had a random scanty distribution from the portal venous drainage to the liver; in fact fluorescence was not equally shared in each liver functional unit, but it was concentrated in some selected sinusoids portal spaces proximal to the portal vein segmentation into the parenchyma probably due to the active Bile salts uptake from the major affluent of the portal system during the digestion accordingly with individual portal flow variations due to alcohol ingestion, lymphatic absorption of the villi, etc.

This experimental observation held the work hypothesis that oral bile salts administration would not have a homogeneous effect upon the whole liver parenchyma, especially when the total amount of pool available had been reduced for enteral loss, diarrhoea, or other impaired absorption conditions.

Thus, our reasonable deduction and claim was that intravenous administration draining a pre-definite amount of biliary salts into the systemic circulation and then reaching the liver via hepatic artery might more extensively, and capillarity, if compared with the fluctuant and accurately unpredictable oral biliary pool, achieve a regular distribution and homogenous uptake by the sinusoid spaces with a more quick and widespread function recover, furthermore the parenteral administration can reach higher concentrations/kg/weight, supposedly, with a faster and better pharmacologic outcome.

II. MATERIALS AND METHODS

We applied to a regularly registered parenteral fluids manufacturing company [SALF Spa, Cenate Sotto (Bergamo, Italy), still existing and producing] and ordered to prepare 500 bottles/500 ml containing 3500 mg of ursodesoxycholic acid (UDCA) and 500 tauro-ursodesoxychilc acid (TUDCA), for a wide pilot clinical trial.

The endpoints of our study have been primarily to observe:

- The safety of high dosages parenteral delivery in normal and sick people,
- The comparison between oral and parenteral administration of BS to relieve the liver insufficiency symptoms and to normalize lab data,
- The proper parenteral administration schedule (cycles of therapy) accordingly with diseases requirement.

Subsequently, depending by steps 1, 2, 3, to eventually define the non-inferiority or the possible superiority of parenteral bile salts administration benefits compared with oral delivery in the most common liver and metabolic diseases, especially in cases where the anatomo-functional GI tract conditions limit or contraindicate the administration by mouth.

Our primary concern has been the safety of the parenteral route at different bile salts concentration starting **from healthy volunteers**.

Inspired to the philosophy of the "*Doctor care yourself Network*" I tried primarily upon myself and 1 month after my totally safe experience, three my healthy doctors 'colleagues spontaneously underwent my identical parenteral treatment (**Table 1**) with the following progressive protocol of parenteral UDCA dosages:

- DAY 0: Baseline lab exams, abdominal & total body echo (thyroid, supra-aortic trunk, hearth, pleaurae, lymph nodes liver stomach pancreas, spleen kidneys, bladder prostate testes). ECG, general cardiovascular visit.
- DAY 1: UDCA infusion 3500 mg in 3 hours
- DAY 6: Visit, abdominal & total body echo, and lab exams
- DAY 8: UDCA 7000 mg in 3 hours
- DAY 20: Visit, abdominal & total body echo, and lab exam
- DAY 40: UDCA 10,500 mg in 5 hours
- DAY 50: Visit abdominal & total body, echo, lab exams

III. RESULTS

The intravenous injections were safe and uneventful even at the highest dosages. Drip velocity was slow, in order to dilute the drug content into the blood stream avoiding chemical damage to venous endothelium. In the follow up, we could safely introduce 500 ml (3500 UDCA mg) in an accelerated short perfusion time (30-45 minutes) without notice any untoward effect.

We delayed each perfusion schedule in order to observe possible ad interim body reactions if any, and observe any effect related to the gut–bile salts enterohepatic circulation.

Even at the highest dosages (10 gr/day) the tolerance was very high; only a very slight episode of headache spontaneously resolved with TUDCA: no change in bowel movements, digestion or other effects, steady reduction of the appetite was noted up to the dosage of 10 gr UDCA and TUDCA.

The biliary salts haematological pool raised from 50 to 180.

We observed a slight shifting of haematological formula toward neutrophilia, no changes in electrophoresis, or lipid metabolism. The glycaemia trend was modestly reduced from 89 to 70-75, being nutritional conditions unchanged.

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Table 1: Hematocrit profile, serum protein electrophoresis

Patient	B.P.	L.R.	U.Y.	L.G.
White blood cells (migl./mmc)	PRE:7.1, POST:8.08	PRE:6.2, POST:9.1	PRE:4.8, POST:6.10	PRE:5.6, POST:8.11
Red blood cells(mil./mmc)	PRE:3.9, POST: 5.31	PRE:4.9, POST: 5.32	PRE:5.1, POST: 6.33	PRE:4.9, POST: 5.34
Hemoglobin (g/dl)	PRE: 11.4, POST: 15.5	PRE: 13.4, POST: 15.6	PRE:11.1, POST: 16.4	PRE: 11.4, POST: 15.8
Hematocrit (%)	PRE: 40.5, POST: 46.9	PRE: 39, POST: 46	PRE: 41, POST: 45.3	PRE: 39.9, POST: 46.12
MCV (fl)	PRE: 71.5, POST: 88.2	PRE: 69.5, POST: 87.3	PRE: 67.5, POST: 85.4	PRE: 69.2, POST: 86.5
MCH (pg)	PRE: 15.1, POST: 29.1	PRE: 12.1, POST: 26.2	PRE: 13.1, POST: 27.3	PRE: 14.5, POST: 28.4
MCHC (g/dl)	PRE: 21.0, POST:33.0	PRE: 23.0, POST:30.1	PRE: 22.0, POST:34.3	PRE: 23.0, POST:34.3
RDW (cv%)	PRE: 11.1, POST: 13.9	PRE: 10.7, POST: 12.9	PRE: 9.1, POST: 12.11	PRE: 11.2, POST: 13.12
Platelets (migl./mmc)	PRE: 195, POST: 221	PRE: 199, POST: 231	PRE: 201, POST: 223	PRE: 192, POST: 218
MPV (fl)	PRE:6.1, POST:9.8	PRE:6.5, POST:9.2	PRE:6.3, POST:9.3	PRE:6.4, POST:9.11
Neutrophils (%)	PRE: 63.2, POST: 67.1	PRE: 62, POST: 66.1	PRE: 63.2, POST: 67.3	PRE: 61.8, POST: 66.4
Lymphocytes (%)	PRE:20.2 , POST: 25.1	PRE:21.1 , POST: 26.2	PRE:20.7 , POST: 25.5	PRE:19.8 , POST: 25.4
Monocytes (%)	PRE:4.1, POST:5.5	PRE:3.8, POST:5.2	PRE:4.0, POST:5.7	PRE:3.9, POST:4.8
Eosinophils (%)	PRE: 0.9, POST:1.4	PRE: 0.8, POST:1.6	PRE: 0.9, POST:1.9	PRE: 1, POST:1.6
Basophils (%)	PRE:0.7, POST:1.0	PRE:0.6, POST:1.0	PRE:0.5, POST:1.1	PRE:0.7, POST:1.3
Total protein (g/dl)	PRE:9, POST:7.6	PRE:8.7, POST:7.5	PRE:8.8, POST:7.8	PRE:9.1, POST:7.9
Albumin (%)	PRE:37, POST:54.9	PRE:38, POST:56.10	PRE:39, POST:55.8	PRE:36, POST:57
Alpha 1 globulin (%)	PRE:4.9, POST:3.6	PRE:4.8, POST:3.7	PRE:4.7, POST:3.9	PRE:4.9, POST:3.9
Alpha 2 globulin (%)	PRE: 14, POST:10.8	PRE: 13, POST:11.9	PRE: 14, POST:12.10	PRE: 13.8, POST:10.9
Beta 1 globulin (%)	PRE:9.2, POST:6.8	PRE:8.7, POST:6.9	PRE:9.2, POST:6.10	PRE:9.1, POST:6.0
Beta 2 globulin (%)	PRE:10, POST:5.6	PRE:9.8, POST:5.5	PRE:10.2, POST:5.7	PRE:10.1, POST:5.9
Gamma globulin (%)	PRE:21, POST:16.3	PRE:20, POST:15.8	PRE:19, POST:16.4	PRE:21, POST:16.3
Carcinoembryonic antigen (CEA) (ng/ml)	PRE:1.4, POST:1.3	PRE:1.4, POST:1.2	PRE:1.2, POST:1	PRE:1.3, POST:1.3
Alpha-Fetoprotein Tumor (AFP) Marker (ng/ml)	PRE:2.6, POST:2.7	PRE:2.5, POST:2.5	PRE:2.4, POST:2.3	PRE:2.6, POST:2.6
Cancer antigen 19-9 (CA 19-9) (U/ml)	PRE:11.3, POST:11.1	PRE:10.9, POST:10.8	PRE:11.3, POST:11	PRE:11.1, POST:10.9
Prostate-Specific Antigen (PSA) (ng/ml)	PRE:1.09, POST:1.03	PRE:1.04, POST:1.04	PRE:1.06, POST:1.05	PRE:1.07, POST:1.06
Creatine Kinase (CK) (U/L)	PRE:89, POST:83	PRE:87, POST:84	PRE:88, POST:83	PRE:87, POST:85
Glucose (mg/dl)	PRE:114, POST:106	PRE:111, POST:107	PRE:116, POST:108	PRE:110, POST:109
Urea (mg/dl)	PRE:38, POST:34	PRE:36, POST:31	PRE:37, POST:32	PRE:38, POST:36
Creatinine (mg/dl)	PRE:0.90, POST:0.88	PRE:0.89, POST:0.65	PRE:0.85, POST:0.70	PRE:0.90, POST:0.70
Estimated glomerular filtration rate (eGFR) (ml/min)	PRE:>64, POST:>60	PRE:>66, POST:>58	PRE:>64, POST:>56	PRE:>67, POST:>60
Uric acid (mg/dl)	PRE:6.6, POST:6.4	PRE:6.5, POST:6.2	PRE:6.6, POST:6.1	PRE:6.4, POST:6.2
Cholesterol (mg/dl)	PRE:190, POST:181	PRE:188, POST:182	PRE:192, POST:183	PRE:190, POST:180
HDL Cholesterol (mg/dl)	PRE:50, POST:48	PRE:51, POST:49	PRE:50, POST:50	PRE:50, POST:51
LDL Cholesterol (mg/dl)	PRE:140, POST:134	PRE:141, POST:135	PRE:149, POST:136	PRE:145, POST:137
Triglycerides (mg/dl)	PRE:109, POST:107	PRE:106, POST:103	PRE:109, POST:109	PRE:108, POST:106
Total bilirubin (mg/dl)	PRE:0.82, POST:0.61	PRE:0.79, POST:0.62	PRE:0.81, POST:0.63	PRE:0.80, POST:0.64
Direct bilirubin (mg/dl)	PRE:<0.5, POST:<0.3	PRE:<0.6, POST:<0.4	PRE:<0.4, POST:<0.2	PRE:<0.5, POST:<0.5
Glutamic-Pyruvic Transaminase -GPT-ALT (U/L)	PRE:20, POST:18	PRE:22, POST:19	PRE:21, POST:20	PRE:23, POST:20
Gamma Glutamil Transferasi - GGT (U/L)	PRE:25, POST:22	PRE:24, POST:23	PRE:25, POST:24	PRE:25, POST:25
Sodium (mEq/L)	PRE:145, POST:142	PRE:146, POST:143	PRE:145, POST:144	PRE:145, POST:145
Potassium (mEq/L)	PRE:5, POST:4	PRE:5, POST:3	PRE:5, POST:5	PRE:4, POST:3
Calcium (mg/dl)	PRE:9.8, POST:9.6	PRE:9.6, POST:9.5	PRE:9.8, POST:9.7	PRE:9.9, POST:9.6
Urine Albumin (mg/g-creat)	PRE:19, POST:15	PRE:20, POST:18	PRE:21, POST:19	PRE:20, POST:19

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IV. DISCUSSION AND CONCLUSIONS

Self-experimental studies by doctors are in our opinion very ethical and recommendable and there are several examples in the history of medicine describing the diagnostic and therapeutic goals achieved by some doctors challenging some discoveries with risk of their personal life.

In 1900 Karl Landstainer classified the blood groups, drawing the blood from himself and six lab co-workers **[5].**

In 1984, Barry Marshall self-performed gastroscopy and duodenal biopsy to detect *Helicobacter pylori* and repeated the procedure after tinidazole treatment to show the intracytoplasmic location of the bacterium **[6]**.

Altman in his book entitled "*Who goes the first? The story of self experimentation in medicine"* described several doctors discoveries in leukaemia, malaria, cancer, HIV, opioids, anaesthetics, yellow fever, typhus e scurvy, ganglionic blockers **[7].**

An outstanding example of courage and stubbornness was the Forssmann behaviour, who first self-catheterized his heart notwithstanding his chief had denied to him to do any experimental procedure on volunteers **[8]**.

Our network "*Doctor-take-care of yourself*", beyond its intrinsic health medical care policy with prevention and cure is intended to optimize the doctor patient relationships and furthermore to place his professional role at the basic level of the patients he cares. In this perspective when sick doctors undergo to pilot trials preceding the phase 1,2,3 official clinical investigations they give a noble warning of being patients themselves with identical aims and hopes, and healing willpower as their clients. These feelings and believes, give a strong support to professional motivation, self-esteem, and encouragement to accomplish the due paradigm of the Hippocratic Oath.

Our bile salts parenteral self-experiment on healthy doctors to define the safety profile dynamics and kinetics of the administered molecules has been a generous example of open-minded colleagues that opens new hopes and perspective in the liver diseases management.

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