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Dose Escalation Phase I Study in Healthy Volunteers to Evaluate the Safety of a Natural Product PM701

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Abstract: Drug discover from natural sources has played an important role in the treatment of cancer and indeed, most new clinical applications of natural materials over the last half century have been applied to combating cancer. Therefore, this study was directed to describe the safety observations following oral administration of an active ingredient PM701 separated from the camel urine which is a clean, sterile product with antiproliferative activity in experimental tumor bearing animals. The study included 14 healthy volunteers with age between 21-48 years (male and female). They were subjected to full history taking, clinical examination and full laboratory tests including liver and kidney functions hematological parameters (Hb, WBCs and platelet count).The same test were done after oral administration of capsules containing PM701. This fraction has been formulated in gelatin capsule containing 300 mg capsule^{-1}. Systemic reactions of normal volunteers after oral administration of capsules containing PM 701over 28 days revealed no adverse effects on the vital organs. Liver and kidney functions showed no abnormalities. Also, complete blood picture revealed normal pattern before and after PM701 treatment. Two patients only developed hyperacidity which was easily been treated. We may conclude that the product MP701 is safe and may be ready to move to the phase II trials on people who all have the same type of cancer or with several different types of cancer aiming to detect which types of cancer PM701 works for and to get more knowledge about side effects and how to manage them.

Key words: Phase I, clinical trial, camel urine, PM701

INTRODUCTION

Cancer is a disease in which the cells fail to respond to the fundamental rules governing cell proliferation and differentiation (Salman and Sartorlli, 2001). There has been a gradual evolution in the philosophy of treatment of cancer (Crown, 1998). Despite, significant advances achieved in cancer treatment, which has relied on surgery, chemotherapy, radiotherapy, hormone therapy and more recently immunotherapy, cancers still a cause of pain and death in our world. The management of malignancies in humans still constitutes a major challenge for contemporary medicine (Coufal *et al*., 2007; He and Liu, 2007; Widodo *et al*., 2007; Feng, 2006). Chemotherapy very often causes severe side effects,

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which are in part a consequence of destruction of normal cells. It was revealed that commonly used anticancer approaches cause significant toxicity in body systems and are responsible for harmful side effects (Khorshid and Moshref, 2006; Moshref *et al*., 2006; Veluri *et al*., 2006). It is of crucial importance that anticancer drugs display antiproliferative activity in tumor cells without affecting normal tissues. Therefore, taking all the above-mentioned evidence into account, the development of novel approaches and effective anticancer strategies is critically needed and eagerly being pursued (Sporn, 1996; Vijayakumar and Hellman, 1997; Chabner and Roberts, 2005). The PM701, a fraction isolated from camel urine is a natural product and it is free of toxicity as observed in our previous investigations. In experimental studies, PM701 treatment found to be safe in mice and rats (Khorshid, 2008). This fact was further confirmed by biochemical investigation of liver, kidney and blood (Khorshid, 2008). Histopathological examination of the organs also revealed non toxic alterations in the organ tissues (Khorshid, 2008).

From the pharmacological point of view, PM701 was found to have a potential antiproliferative activity against human lung cancer cell lines *in vitro* and against Leukemia L1210 *in vivo* (Khorshid and Moshref, 2006).

The purpose of this study was directed to evaluate the drug's safety in health volunteers. Clinical trail has been performed on human volunteers. They received capsules containing 300 mg and observed every two weeks and for 4 months.

The dose given was increased step-wise until the Maximum Tolerated Dose (MTD) has been reached and the Dose Limiting Toxicity (DLT) was established.

MATERIALS AND METHODS

This study has been conducted after extensive experimental work and during the period between January 2008-2010.

Tested Agent

PM701, is a natural product; which in our earlier studies have shown to be clean, sterile and free of toxicity in a wide variety of experiments (Khorshid, 2008).

The natural product from PM701, has been formulated in the form of hard vegetation gelatin capsule. Each capsule contained 300 mg. Only clinically fit volunteers received 3 capsules day^{-1} in the first week and 5 capsules day^{-1} for the second week and/or 8 capsules day^{-1} for third weeks and 10 capsules day^{-1} for four months. Clinical examinations and other investigations were performed on day 0, 14 and 21 from the start of drug therapy and finally on the day of termination of drug (four months later).

Volunteers and Trials

Limited clinical trials on 14 individuals were conducted in this study.

The nature of the drug was explained and written consent was signed by each volunteer. All volunteers were subjected to medical history and clinical examination. Those having the history of allergic condition such as: asthma, urticaria, psychiatric disorders were excluded from the study. Likewise people with dyspepsia, gastric ulcer or duodenal ulcer; pregnancy or breast feeding were also not considered for the present trials. It was assured that all participating in this study meet inclusion and exclusion criteria. All 14 people were carefully selected for the trials.

Dose of PM 701

After clinical examinations and investigations, volunteers received PM701 in capsule form according to the following schedule:

- 3 capsules daily/week 1
- 5 capsules daily/week 2
- 8 capsules daily/week 3
- 10 capsules daily start in week 4 and continued for 4 months

Biochemical Evaluations

All volunteers were exposed to biochemical analysis before and after PM701 treatment These assessments included, complete differential blood count, serum analysis for albumin, total bilirubin, alkaline phosphates, alanine transaminase (ALT), aspartate transaminase (AST), creatinine, electrolytes and sugar.

Other examinations were done if required such as abdominal sonography and serum pregnancy test of a child bearing potentials was done as when required.

The therapy continued to a maximum of 16 weeks and all laboratory investigations were recorded.

Prophylactic Measure

The following measures are strongly suggested to reduce the change of renal complication with treatment: Patients should drink plenty amount of water with camel milk

RESULTS AND DISCUSSION

The study was approved by the Institutional Review Board of the King Abdulaziz University (298-09 at 1/16/2008) and was conducted in our hospital under contact medical supervision. All patients provided written informed consent.

PM701 Production

Formulation of Powder Mixture

The active ingredient is mixed with appropriate amount of the diluents and lubricant in various portions, the formula that gives the optimal flow properties and highest active ingredient content is selected. The active ingredient powder and excipients are mixed by light tribulation (geometric dilution). The blend is transferred to the mixer, mixing for 3-5 h. Random samples are taken for analysis of uniformity of content.

Filling of the Powder into the Hard Gelatin Capsules

The capsules are prepared using hand-operated capsules machine operated as specified by the manufacturer operation manual. The weight required to fill the specified number of capsule is determined and amount of powder exceed the required weight by 5% is used.

The finished capsules are cleaned by shaking with powdered NaCl, rolled on sterilized cloth covered surface, then subjected to a stream of lightly compressed air.

The capsules (10-20 capsules) are baked into the sterilized clean glass container (with moisture adsorption packets).

Safety

The PM701 in a capsule form was well tolerated by all patients. There were no serious adverse events observed during the study and no patient withdrew from the study due to

Table 1: General characteristics of the volunteers

Characteristics	Values
Total	14
Age	21-48 years
Sex	Male and female (8 and 4)
Nationality	Saudi Arabian

Table 2: Clinical laboratory findings of normal volunteers at zero time (control group)

	Volunteers														
Tests	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Average (Mean±SD)
CBC (Blood)															
HB (14-18 g dL^{-1})	15.9	11.1	14.1	13.4	11	15.9	14.3	12.2	13	15.8	14.4	12.8	16.2	14.8	15.8±2.1
WBC (4-12 K μL^{-1})	11.5	5.0	7.9	7.5	4.27	4.4	7.9	11.1	4.7	5.8	5.2	8.6	6.3	3.6	10.5±1.1
PLTx10-3 (150-450 K μL^{-1})	326	374	282	251	350	250	241	237	239	227	247	397	306	149	248.0±5.5
Liver function (μL^{-1})															
ALP (50-136)	161	79	91	68	-	36.6	-	68	-	59	151	70	-	26.4	67.0±3.3
GGT (5-85)	54	47	17	19	19	-	-	21	-	-	35	19	-	25.5	38.0±1.0
AST (15-37)	22	23	26	16	14	25.8	-	19	-	-	30	21	20	16.8	22.3±1.1
ALT (30-65)	75	29	46	34	32	27.3	77	40		23	68	41	40	26	43.0±2.3
Kidney functions (μL^{-1})															
Urea (3.6-18 mmol L^{-1})	-	7.14	4.9	2.2	-	4.8	-	-	-	6.2	-	-	5.3	10.3	10.01±1.9
Creatinine (44.2-79.56 μmol L^{-1})	70	50.38	87	51	106	108	106.9	-	-	87	-	-	-	79.6	77.3±1.1
Uric acid (155-428 μmol L^{-1})	364	255.7	-	-	-	359	-	190.3	-	-	294	217	256	274	359.0±3.3

an adverse event caused by the product PM701 (Table 3). Four patients have been suddenly withdrawn from the study before starting the analysis due to their travel during the period of continuous investigation.

Table 1 summarized the biochemical investigations of the healthy volunteers before entering the actual study and treated as control. The same tests were repeated just after receiving the PM701 on day 14 and 21 and finally after four months at the termination of experiments. The results have been summarized in Table 3. A separate Table 4 shows a comparative study of control and treated individuals. This study reports the effect of oral administration of natural product PM701 in humans. Although, the group sizes in the study do not allow good statistical evaluation, the high percentage of safety of this product suggests its possible applicability in large scale study. Most of the observations fall within the normal range of each test.

The drug was safe in the normal volunteers and it could be applicable for phase II studies. No undesired change or reaction in the body chemistry was detected as shown in Table 2. All the vital organs studied such as liver, kidney and bone marrow showed normal functions before (Table 2) and after PM701 administration (Table 3). However, one case reported initial slight increase in liver enzymes which came to normal range shortly after treatment without further complication till the end. A comparison between normal and treated volunteers showed insignificant difference. Clinical trials are conducted to allow safety and efficacy data to be collected for new drugs. Our trials were conducted on normal volunteers, since a satisfactory information has been gathered on the efficacy and quality of non-clinical safety of PM701 (Korshid, 2008).Although, people taking part in phase I trials often have advanced cancer and have usually had all the treatment available to them, we conducted our study using healthy volunteers as camel urine (PM701) is traditionally used in our country safely as folk remedy for many disease (Al-Rawais, 2002).

Table 3: Clinical laboratory findings of normal volunteers after treatment with PM701 (at 0, 14 and 28 days)

	Volunteers										
Tests	1	2	3	4	5	6	7	8	9	10	Average
CBC											
HB											
0	15.3	10.6	14.2	-	10.3	15.2	15	11.4	13.1	15.5	12.060
14	15.6	10.6	14	-	10.6	-	15.4	12.6	-	15.7	9.45
28	-	10.7	14	12.9	10.9	-	-	12	13.7	-	7.42
WBC											
0	10.9	5.6	8.3	-	4.1	4.7	6.1	7.6	4.1	4.8	5.62
14	12.3	6.0	7.6	-	5.7	-	6.9	6.5	-	5.7	5.07
28	-	-	7.4	9.4	3.6	-	-	8.5	3.8	-	3.27
PLT											
0	278	302	307	-	326	265	190	252	255	288	246.3
14	272	438	308	-	317	-	199	295	-	238	206.70
28	-	278	279	254	309	-	-	308	218	-	164.6
Liver											
ALP											
0	150	76	94	73	90	-	-	56	47	64	65.0
14	139	69	96	82	83	-	-	61	-	63	59.30
28	-	77	87	90	94	51.4	-	55	51	-	50.540
GGT											
0	47	36	15	13	20	-	-	18	-	-	14.90
14	38	43	11	15	17	-	-	23	-	-	14.70
28	-	49	8	17	25	-	-	22	-	-	12.10
AST											
0	22.4	23	26	-	25.8	16	14	19	-	-	14.620
14	28	15	24	-	19.7	19	17	14	-	-	13.670
28	22	17	23	-	-	17	19	20	-	-	11.80
ALT											
0	75	29	46	77	27.3	34	32	40	-	33	39.33
14	72	13	46	78	-	34	32	33	8	-	31.60
28	58	43	36	78	-	37	41	38	-	-	33.10
Kidney											
Urea											
0	-	7.14	4.9	-	4.8	2.2	-	-	-	6.1	2.524
14	-	6.78	-	-	3.6	-	-	-	-	-	1.0380
28	6.1	6.069	-	-	-	-	-	-	-	-	1.2169
Creatinine											
0	70	50.38	87	106,9	108	51	106	-	55	80	71.428
14	-	57.64	-	91.05	73	-	-	-	57	-	27.869
28	68	44.2	-	106.0	-	-	-	-	-	-	21.82
Uric acid											
0	364	255.7	-	-	359	-	-	190.3	-	-	116.9
14	-	243.8	423	-	273	176	440	202.2	-	-	175.8
28	374	196.2	431	-	317	140	422.3	160.5	-	-	204.1

Table 4: Comparative study of control and treated volunteers after 28 days of treatment

Organ	Test	Control average	Treated average	Std. Error	$p \geq 0.5$
Blood	HB	12.060	9.4500	2.7050	0.343
	WBC	5.620	5.0700	1.6230	0.737
	PLT	246.300	206.7000	59.8700	0.867
Liver	ALP	65.000	59.3000	19.3080	0.770
	GGT	14.900	14.7000	7.2500	0.978
	AST	14.620	13.6700	4.6810	0.552
	ALT	39.330	31.6000	11.4470	0.591
Kidney	Urea	2.514	1.0380	1.1683	0.217
	Creatinine	71.428	27.8690	16.2885	0.013
	Uric acid	116.900	175.8000	75.3940	0.441

Although, this study on healthy volunteers was limited (14 patients),all volunteers showed safety and tolerability of the MP701. Few individuals showed some gastrointestinal

disturbance, especially hyperacidity and increase in sleeping tendency after initiation of the therapy. No significant change in liver and kidney functions or abnormal profile of complete blood count have been observed.

As we expect, for any new drug, the possibility of severe anaphylactic or idiosyncratic reactions have not been ignored, no such adverse effects were observed.

The pharmacological and toxicological studies of the product PM701 in animal models showed no any toxic or harmful effect on different vital organs (Khorshid, 2008). So, we may conclude that PM701 is clean sterile product which has the ability to inhibit the proliferation of cancer cells both *in vitro* and *in vivo* (Khorshid and Moshref, 2006) and has no adverse effect either on animals species and or human health volunteers. So, moving to phase II trial on advanced cancer patients might be advisable to explore the efficacy of PM701 as anticancer agent.

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