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EFFECT OF ISONIAZID ON PERFORMANCE

By

Richard O. Nossaman, SP/5, U.S. Army

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U. S. ARMY AEROMEDICAL RESEARCH LABORATORY

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This research effort would not have been possible without those civilian instructor pilots who willingly cooperated and gave freely of their personal time.

ABSTRACT

Nine aviators who converted from negative to positive on a tuberculosis tine test performed a variety of laboratory tests given before, during and after INH therapy. INH was administered prophylactically at dosage levels of 300 mg. per day. The tasks consisted of reaction time (auditory and visual), rotary pursuit tracking, mental multiplication and digit span. The data did not indicate that the drug adversely affected performance, on any of the tasks utilized.

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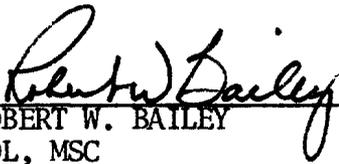

ROBERT W. BAILEY
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EFFECT OF ISONIAZID ON PERFORMANCE

INTRODUCTION

This study represents one part of a tripartite study carried out in conjunction with Lyster Army Hospital and the Neurology Branch of the US Army Aeromedical Research Laboratory. The study was initiated upon request of the Aviation School when a number of civilian instructor pilots became tuberculin converters. They were subsequently placed on isoniazid (INH), a prophylactic drug for tuberculosis. Typically, it has been the policy of the US Army to recommend this treatment for one year if tuberculin skin tests convert from negative to positive. During this period, converters on flying status serving the US Army are normally grounded. This action was called into question at Fort Rucker for two reasons: 1) the manpower loss, and 2) the lack of evidence of debilitating effect of INH on performance.

The Aviation Psychology Division was asked to determine if this chemotherapy at dosage levels of 300 mg. per day had an effect on performance. A review of the literature indicated isoniazid at some dosage levels was said to produce side effects of: peripheral neuropathy; constipation; diarrhea; peresthesia; hyperflexia; muscular twitch; delay in micturition; convulsions; psychoses; fatigue; impairment of concentration memory and depression^{1,2,3,4,5,6,7,8}.

With respect to performance, a study by Olsen and Torning⁹ demonstrated differences between scores on a "subtle test" for patients receiving INH therapy. These differences occurred between scores taken before treatment began and scores taken two months into the treatment period. No differences were found between pre-treatment and post-treatment scores. They contended this test demonstrated a

tendency for INH patients to forget things in the peripheral part of the attention sphere. Thus, they concluded, "Although the reported psychological side effects do not contraindicate the use of isoniazid in tuberculous patients, we feel they speak in favor of a certain caution in using isoniazid prophylactically on a large scale in healthy people." Isoniazid in this study was administered at dosage levels of 4 mg. per kilogram of body weight combined with para-aminosalicylate (PAS) at 200 mg. per kilogram of body weight. PAS was discounted as producing the above effects based on previous observations, by the authors, of patients treated with streptomycin (SM) and PAS.

A study by Simon¹⁰ indicates that isoniazid therapy does not have an adverse psychological effect. Simon administered the Rorschach, Minnesota Multiphasic Personality Inventory (MMPI), Scale of Inner Maladjustment (SIM), Bell Adjustment Inventory, An Inventory of Factors STDCR, The Guilford-Martin Inventory of Factors (GAMIN), Wechsler Memory Scale and Digit Symbol, to patients before INH therapy and again six months after treatment was initiated. None of these psychological tests revealed any negative effects. However, some positive effects were noted. The author concluded, "Most essential is that the results of the study bear out the general hypothesis that patients under Isoniazid therapy do not show deleterious psychological effects."

Theodore and Wolff¹¹, in a very well controlled study, did not find any drug effect when comparing school ratings between approximately 800 children taking isoniazid and 800 taking a placebo. Nor, did they find that school performance was related to amount of medication prescribed. They concluded if isoniazid has any effect on the mental ability of children, it was too slight to be detected by their study.

The object of the present study was to measure the performance of a group of instructor pilots taking isoniazid. Performance measures were taken on a number of laboratory tasks to determine if they would be affected by this chemotherapy.

METHOD

Subjects

Subjects were nine rotary-wing aviator instructors between the ages of 33 and 58. This group had a mean age of 45.

Performance Tasks

Rotary Pursuit Tracking (RPT). The rotary pursuit tracking device utilized a twelve inch disc with a round target, one inch in diameter placed one inch from the edge. The twelve inch disc was rotated at 26 rpm and Time on Target (TOT) was measured in seconds to the nearest tenth of a second on a Cramer Timer. All tracking trials lasted two minutes. Tracking took place with no ancillary tasks and also while performing mental multiplication and digit span.

Mental Multiplication (MV). This task consisted of presenting a series of five multiplication problems from a slide projector. Problems were projected directly in front of the subject. The exposure time for each problem was held constant at four seconds. After this four second period, the problem was removed and the subject gave his answer. Time to respond was measured by a Standard Electric Timer. This timer measured in 1/100 of a second. Measurements were also taken as to the accuracy of response. This task was performed during a two minute tracking trial.

Digit Span Visual (DV). This task required the subject to repeat from memory visually presented digits, while tracking. The presentation mode was the same as that utilized with the visual multiplication problems. The span of digits was seven in length and a series of five were given to each subject. Measurements were taken with regard to response time and accuracy of response.

Mental Multiplication Auditory (MA). In this task, the subject received five mental multiplication problems aurally. Each problem took 1.5 seconds to present after which the subject gave his answer. Time to respond was recorded as well as errors in response. Problems were delivered over head-phones which had 46 db SPL of pink noise at all times except when problems were given. This task was done simultaneously while tracking.

Digit Span Auditory (DA). This task was administered in the same manner as the MA task described above with the exception that, instead of multiplication, a series of seven digit spans were delivered. Each digit span took seven seconds to present and all were presented during a two minute tracking trial.

Visual Reaction Time (VRT). This task consisted of responding to a red light which was energized randomly at inter-signal intervals of three, four, and five seconds. When the light came on, a clock started which ran until the subject responded by pushing a hand-held micro-switch. This response terminated the light and the clock also indicated the start time of the next inter-signal interval.

Reaction time was measured to the nearest 1/100 of a second by a Standard Electric Timer. The subjects did not track while performing this task.

Auditory Reaction Time (ART). This task was administered in the same manner as the visual task described above except that in this case the stimulus was a 46 db SPL pink noise signal delivered through the head-phones.

Procedure

Subjects were tested several days before beginning chemotherapy. This pre-trial constituted the control trial. Subjects were seated in an experimental room and given a standardized set of instructions. The first task was visual reaction time followed by auditory reaction time. The VRT task consisted of 13 trials. Three practice trials followed by ten test trials. The ART was administered in the same manner. After these tests were completed, standardized instructions were given for the tracking tasks. Before the testing session began, a two minute practice trial was given. Following this, a two minute tracking trial with no ancillary tasks was initiated. This was followed by a one minute rest period after which tracking tasks with mental multiplication and digit span were given. Preceding each trial were practice trials. Between the multiplication and digit span tasks which were presented both visually and aurally, one minute rest periods were given. All tracking tasks were two minutes in length. The total test time per person was approximately 35 minutes. After Trial I, the same procedure was repeated on: Day 43 after therapy started (Trial II); Day 181 of treatment period (Trial III); Day 300 of treatment period (Trial IV); and seven days after cessation of the drug treatment (Trial V).

RESULTS

One way analyses of variance with repeated measures on one factor were chosen over two factor analyses of variance treating subjects as a factor. This was done because a review of the data revealed no systematic trends for individual subjects. Therefore, for the purpose of this study, trial differences for the group were of primary importance. The significance level chosen was .01 or less for all tests. Each score used in the analyses of the auditory and visual, digit span and mental multiplication data is a mean of five trials. Scores used in the reaction time analyses are based on the mean of ten measures and the missed responses and tracking scores

used are based on one measure per subject. Newman-Keuls a posteriori tests were performed on data found to be significant in the analyses of variance.

Tracking (Time on Target Scores - TOT). TOT scores across the trials for tracking under the conditions of: no ancillary tasks (CT); mental multiplication with problems presented visually (TMV); digit span with digits presented visually (TDV); and performing digit span with digits presented aurally (TDA), were found to be significant to .01 level, as indicated in Tables 1, 2, 3, and 4.

Table 1.

Summary of Analysis of Variance
Control Tracking - CT

Source	SS	df	MS	f
Between Subjects	911.607	8		
Within Subjects	3070.932	36		
Trials	2113.737	4	528.434	17.67**
Residual	957.195	32	29.912	
Total	3982.539	44		

**p < .01

Table 2.

Summary of Analysis of Variance
Tracking - TMV

Source	SS	df	MS	f
Between Subjects	2043.404	8		
Within Subjects	3030.296	36		
Trials	1761.420	4	440.355	11.11**
Residual	1268.867	32	39.652	
Total	5073.700	44		

**p < .01

Table 3.
Summary of Analysis of Variance
Tracking - TDV

Source	SS	df	MS	f
Between Subjects	2584.470	8		
Within Subjects	3073.500	36		
Trials	1732.788	4	433.197	10.34**
Residual	1340.712	32	41.897	
Total	5657.970	44		

**p < .01

Table 4.
Summary of Analysis of Variance
Tracking - TDA

Source	SS	df	MS	f
Between Subjects	1114.567	8		
Within Subjects	1362.144	36		
Trials	495.657	4	123.914	4.58**
Residual	866.487	32	27.078	
Total	2476.711	44		

**p < .01

Table 5 indicates that TOT-TMA or tracking while performing mental multiplication with problems presented aurally, was not significant at the .01 level.

Table 5.
Summary of Analysis of Variance
Tracking - TMA

Source	SS	df	MS	f
Between Subjects	1103.604	8		
Within Subjects	1466.844	36		
Trials	464.739	4	116.185	3.71
Residual	1002.105	32	31.316	
Total	2570.448	44		

**p < .01

Post-hoc tests performed on these significant results can be found in Tables 6, 7, 8, and 9.

Table 6.
Tests on Differences Between Totals
Control Tracking - CT

Ordered Trials	I	III	II	IV	V	
Totals	859.4	986.6	1002.0	1016.8	1031.0	
I	859.4	-	127.2**	142.6**	157.4**	171.6**
III	986.6	-	15.4	30.2	44.4	
II	1002.0		-	14.8	29.0	
IV	1016.8			-	14.2	
V	1031.0				-	
Truncated range r		2	3	4	5	
q _{.99} (r,32)		3.89	4.45	4.80	5.05	
\sqrt{nMSres} q _{.99} (r,32)		63.83	73.02	78.77	82.87	

**p < .01

Table 7.

Tests on Differences Between Totals
Tracking - TMV

Ordered Trials	I	III	II	V	IV	
Totals	810.2	899.9	933.5	950.7	970.2	
I	810.2	-	89.7**	123.3**	140.5**	160.0**
III	899.9	-	33.6	50.8	70.3	
II	933.5		-	17.2	36.7	
V	950.7			-	19.5	
IV	970.2				-	
Truncated range r		2	3	4	5	
$q_{.99}(r, 32)$		3.89	4.45	4.80	5.05	
$\sqrt{nMSres} q_{.99}(r, 32)$		73.48	84.06	90.67	95.39	

**p < .01

Table 8.

Tests on Differences Between Totals
Tracking - TDV

Ordered Trials	I	III	II	V	IV	
Totals	781.5	881.3	911.5	924.7	936.1	
I	781.5	-	99.8**	130.0**	143.2**	154.6**
III	881.3	-	30.2	43.4	54.8	
II	911.5		-	13.2	24.6	
V	924.7			-	11.4	
IV	936.1				-	
Truncated range r		2	3	4	5	
$q_{.99}(r, 32)$		3.89	4.45	4.80	5.05	
$nMSres q_{.99}(r, 32)$		75.54	86.42	93.22	98.07	

**p < .01

Table 9.

Tests on Differences Between Totals
Tracking - TDA

Ordered Trials	I	II	III	V	IV	
Totals	932.6	971.0	985.2	1006.1	1018.2	
I	932.6	-	38.4	52.6	73.5	85.6**
II	971.0	-	14.2	35.1	47.2	
III	985.2	-	-	20.9	33.0	
V	1006.1	-	-	-	12.1	
IV	1018.2	-	-	-	-	
Truncated range r		2	3	4	5	
$q_{.99} (r,32)$		3.89	4.45	4.80	5.05	
$\sqrt{nMSres} q_{.99} (r,32)$		60.72	69.46	74.93	78.83	

**p < .01

For CT-TOT it can be seen that Trials V, IV, II, and III are significantly different from Trial I, while not differing one from another. In the case of TMV-TOT, Trials IV, V, II, and III differed significantly from Trial I and not from one another. The post-hoc test for TDV-TOT indicates that Trials IV, V, II, and III differed from Trial I and were not different from one another. For TDA-TOT Trial IV differed from Trial I with no other differences present.

Mental Multiplication: Mental multiplication presented visually (MV) and aurally (MA) was performed while tracking. MV and MA scores (time to respond) analyses can be found in Tables 10 and 11.

Table 10.

Summary of Analysis of Variance
 Multiplication Visual - MV

Source	SS	df	MS	f
Between Subjects	160.982	8		
Within Subjects	136.054	36		
Trials	45.877	4	11.469	4.07**
Residual	90.177	32	2.818	
Total	297.036	44		

**p < .01

Table 11.

Summary of Analysis of Variance
 Multiplication Auditory - MA

Source	SS	df	MS	f
Between Subjects	122.849	8		
Within Subjects	54.726	36		
Trials	16.608	4	4.152	3.49
Residual	38.118	32	1.191	
Total	180.620	44		

**p < .01

MV across trials was significant at the .01 level while MA was not found to be significant. The post-hoc test for MV did not detect any significant trial differences. Analyses for errors in responding for MV and MA can be found in Tables 12 and 13, neither of which yielded any significant trial effects.

Table 12.

Summary of Analysis of Variance
Missed Responses - MV

Source	SS	df	MS	f
Between Subjects	49.20	8		
Within Subjects	18.00	36		
Trials	2.76	4	.69	1.44
Residual	15.24	32	.48	
Total	67.20	44		

**p < .01

Table 13.

Summary of Analysis of Variance
Missed Responses - MA

Source	SS	df	MS	f
Between Subjects	30.58	8		
Within Subjects	26.40	36		
Trials	6.09	4	1.52	2.42
Residual	20.31	32	.63	
Total	56.98	44		

**p < .01

Digit Span: Digit Span measures were taken while the subjects tracked, and were in two forms, time to respond and correctness of response. The digits were presented visually (DV) and aurally (DA). Analysis of variance Tables 14 and 15 indicate that there were no significant trial effects for the time measures.

Table 14.

Summary of Analysis of Variance
Digit Span Visual - DV

Source	SS	df	MS	f
Between Subjects	16.971	8		
Within Subjects	10.932	36		
Trials	.769	4	.192	.60
Residual	10.163	32	.318	
Total	27.903	44		

**p < .01

Table 15.

Summary of Analysis of Variance
Digit Span Auditory - DA

Source	SS	df	MS	f
Between Subjects	126.208	8		
Within Subjects	14.485	36		
Trials	2.189	4	.547	1.42
Residual	12.296	32	.384	
Total	140.693	44		

**p < .01

Tables 16 and 17 indicate in the same manner that there were no significant trial effects for missed responses.

Table 16.

Summary of Analysis of Variance
Missed Responses - DV

Source	SS	df	MS	f
Between Subjects	44.84	8		
Within Subjects	40.40	36		
Trials	4.13	4	1.03	.91
Residual	36.27	32	1.13	
Total	85.24	44		

**p < .01

Table 17.

Summary of Analysis of Variance
Missed Responses - DA

Source	SS	df	MS	f
Between Subjects	71.20	8		
Within Subjects	31.60	36		
Trials	6.36	4	1.59	2.01
Residual	25.24	32	.79	
Total	102.80	44		

**p < .01

Reaction Time: The analysis of visual reaction time (VRT) scores across trials was not significant as can be seen in Table 18.

Table 18.

Summary of Analysis of Variance
Visual Reaction Time - VRT

Source	SS	df	MS	f
Between Subjects	.011	8		
Within Subjects	.431	36		
Trials	.047	4	.012	1.0
Residual	.384	32	.012	
Total	.442	44		

**p < .01

However, the auditory reaction time (ART) scores were significant at the .01 level (Table 19).

Table 19.

Summary of Analysis of Variance
Auditory Reaction Time - ART

Source	SS	df	MS	f
Between Subjects	.014	8		
Within Subjects	.030	36		
Trials	.016	4	.004	8.53**
Residual	.015	32	.0005	
Total	.044	44		

**p < .01

Post-hoc tests on the auditory reaction time (Table 20) reveal trials IV and V differed from Trial I.

Table 20

Tests on Differences Between Totals
Auditory Reaction Time - ART

Ordered Trials		I	II	III	V	IV
	Totals	1.328	1.475	1.495	1.755	1.756
I	1.328	-	.147	.167	.427**	.428**
II	1.475		-	.020	.280	.281
III	1.495			-	.260	.261
V	1.755				-	.001
IV	1.756					-
Truncated range r			2	3	4	5
q _{.99} (r,32)			3.89	4.45	4.80	5.05
$\sqrt{nMS_{res}}$ q _{.99} (r,32)			.261	.298	.322	.335

**p < .01

Analyses of false responses indicated that false response to visual and auditory signals were not significant over trials (Tables 21 and 22).

Table 21.

Summary of Analysis of Variance
False Responses - VRT

Source	SS	df	MS	f
Between Subjects	57.78	8		
Within Subjects	118.80	36		
Trials	25.24	4	6.31	2.16
Residual	93.56	32	2.92	
Total	176.58	44		

**p < .01

Table 22.

Summary of Analysis of Variance
False Responses - ART

Source	SS	df	MS	f
Between Subjects	104.40	8		
Within Subjects	192.40	36		
Trials	59.69	4	14.92	3.60
Residual	132.71	32	4.15	
Total	296.80	44		

**p < .01

DISCUSSION

Inasmuch as many tests were performed, the confidence level for any one test when viewing the study in its entirety was not .99. Thus, one cannot place too much emphasis on any one test showing significance. Another thing that must be remembered is the fact that this was an experiment of opportunity and as such, controls were not always as rigorous as one might desire. For example, each subject was not tested at the same time of day, nor was there a control group. The post-hoc tests on control tracking (no ancillary tasks), tracking while performing visually presented multiplication problems, and tracking while performing digit span presented visually, had the same net result. Trial I was in every case significantly different from subsequent trials and in all cases indicated the poorest performance. One explanation of this, can be made in terms of learning, that is to say, learning took place in tracking performance, which would indicate that the practice trials did not bring learning to an asymptote. If this were the case, it can be concluded that if there were a decrement produced by the drug, it was not of sufficient magnitude to offset this learning effect. In addition, the other trials cannot be considered significantly different from one another indicating that no deleterious drug effect occurred, cummulative, nor were there withdrawal effects. Another explanation of the results could be made in terms of the drug improving performance. This would be tenuous without further research and would not explain why the performance of Trial V (after cessation of the drug) did not differ from Trials II, III, and IV. The task of tracking while performing digit span

presented aurally, had a lesser trial effect with only Trial IV being statistically significant from Trial I. If the hypothesis is accepted that learning contributed to trial effects, this is not a wholly unexpected result. For aviators are quite used to receiving and responding to auditory information while performing tracking tasks, so learning effects would be expected to be less. In any event, this result indicates no drug effect. The above explanation also serves to elucidate the nonsignificant trial effect for tracking while performing the mental multiplication presented aurally. In general, if the drug did effect one's ability to attend to tasks as might be suspected from some of the literature⁹, this was not found in the case for the tracking tasks used in this study, because Trial I with no drug was never significantly better than subsequent trials with or without drug.

Scores on multiplication of visually presented problems yielded a significant trial effect, but the Newman-Keuls procedure did not discriminate between trials. However, in terms of absolute values, Trials III, IV, and V produced shorter response times than Trials I and II. Though not statistically significant, these values support the position of a nondetrimental drug effect. Multiplication and digit span presented aurally and digit span presented visually were not significant across trials which would indicate no drug effect for these kinds of memory and mental manipulation tasks. In addition, missed responses, on digit span and mental multiplication for both aural and visual presentation produced no significant trial effects. This would indicate that the drug did not impair mental performance in terms of correctness of response over trials.

Auditory reaction times indicated a significant trial effect, with Trials IV and V producing significant slower reaction times than Trial I. This result is best explained in terms of the false response data for auditory reaction time. The data, though not statistically significant, revealed that 27 false responses were associated with Trial I. This would indicate a high anticipatory reaction resulting in faster responses while producing more false responses or responding before the signals appeared. On the other hand, Trials IV and V indicated seven and zero false responses respectively, indicating that on the latter trials subjects waited for a signal before responding which would lead to longer reaction times but more accuracy. The mean reaction time difference between Trial I and IV or V is .047 seconds. Though statistically significant, in most cases it is not practically significant and in light of the reduction of false responses, which at a minimum is 20, indicates that performance improved on the latter trials. It is unlikely that the drug produced this result since Trials IV and V are not different, and Trial V occurred after cessation of the drug. A better explanation for such behavior might be

offered in terms of familiarity with the task which could have lead to the extinction of trying very hard to be "super-quick." Visual reaction time as well as false responses to aurally and visually presented signals were not significantly different over trials indicating no performance decrement as a function of drug treatment.

CONCLUSION

Performance on the tasks utilized in this investigation was not adversely affected by INH taken prophylactically at dosages of 300 mg. daily.

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